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GmbH, Ingelheim (DE)(21) **Appl. No.:** 10/719,369(22) **Filed:** Nov. 21, 2003**Related U.S. Application Data**(60) Provisional application No. 60/430,796, filed on Dec.
4, 2002.(57) **ABSTRACT**

Disclosed herein are compounds of formula $Ar^1-X-W-Ar^2$ wherein Ar^1 and Ar^2 represent aryl groups characterized generally as aromatic heterocycles (e.g. imidazolyl or tetrazolyl) or carbocycles (e.g. phenyl or naphthalenyl); the aryl groups are optionally substituted or fused with other heterocycles or carbocycles; the aryl groups can bear substituents such as alkyl, halo or O-alkyl. X is a heteroatom, a valence bond or an optionally substituted divalent methylene, and W represents a spacer; typical spacers include divalent alkylene or alkylene-amido, -amido or -oxy radicals, which may optionally be substituted (e.g. hydroxyl or oxo). A typical compound is a derivative of 2-(N-naphthalenyltetrazolylthio)-N-(2-nitrophenyl)acetamide. The compounds have inhibitory activity against Wild Type and single or double mutant strains of HIV.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

RELATED APPLICATIONS

[0001] Benefit of U.S. Provisional Application No. 60/430,796, filed Dec. 4, 2002 is hereby claimed.

TECHNICAL FIELD OF THE INVENTION

[0002] The invention relates to compounds and pharmaceutically acceptable salts thereof, their use, either alone or in combination with other therapeutic agents, in the treatment or prophylaxis of HIV infection, and to pharmaceutical compositions comprising the compounds that are active against HIV wild type and NNRTI resistant mutants.

BACKGROUND OF THE INVENTION

[0003] The disease known as acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), particularly the strain known as HIV-1. In order for HIV to be replicated by a host cell, the information of the viral genome must be integrated into the host cell's DNA. However, HIV is a retrovirus, meaning that its genetic information is in the form of RNA. The HIV replication cycle therefore requires a step of transcription of the viral genome (RNA) into DNA, which is the reverse of the normal chain of events. An enzyme that has been aptly dubbed reverse transcriptase (RT) accomplishes the transcription of the viral RNA into DNA. The HIV virion includes copies of RT along with the viral RNA.

[0004] Reverse transcriptase has three known enzymatic functions; it acts as an RNA-dependent DNA polymerase, as a ribonuclease, and as a DNA-dependent DNA polymerase. Acting as an RNA-dependent DNA polymerase, RT transcribes a single-stranded DNA copy of the viral RNA. Acting as a ribonuclease, RT destroys the original viral RNA, and frees the DNA just produced from the original RNA. Finally, acting as a DNA-dependent DNA polymerase, RT makes a second, complementary DNA strand, using the first DNA strand as a template. The two strands form double-stranded DNA, which is integrated into the host cell's genome by another enzyme called integrase.

[0005] Compounds that inhibit the enzymatic functions of HIV-1 reverse transcriptase will inhibit replication of HIV-1 in infected cells. Such compounds are useful in the prevention or treatment of HIV-1 infection in human subjects, as demonstrated by known RT inhibitors such as 3'-azido-2',3'-dideoxythymidine (AZT), 2',3'-dideoxyinosine (ddI), 2',3'-dideoxycytidine (ddC), d4T, 3TC, Nevirapine, Delavirdine, Efavirenz, Abacavir, and Tenofovir, the main drugs thus far approved for use in the treatment of AIDS.

[0006] As with any antiviral therapy, use of RT inhibitors in the treatment of AIDS eventually leads to a virus that is less sensitive to the given drug. Resistance (reduced sensitivity) to these drugs is the result of mutations that occur in the reverse transcriptase segment of the pol gene. Several mutant strains of HIV have been characterized, and resistance to known therapeutic agents is believed to be due to mutations in the RT gene. One of the more commonly observed mutants clinically for the non-nucleoside reverse transcriptase inhibitors, is the K103N mutant, in which a lysine (K), at codon 103, has been mutated to a asparagine

(N) residue. Other mutants, which emerge with varying frequency during treatment using known antivirals, include single mutants Y181C, G190A, Y188C, and P236L, and double mutants K103N/Y181C, K103N/P225H, K103N/V108I and K103N/L100L.

[0007] As antiviral use in therapy and prevention of HIV infection continues, the emergence of new resistant strains is expected to increase. There is therefore an ongoing need for new inhibitors of RT, which have different patterns of effectiveness against the various resistant mutants.

[0008] The compounds of this invention can be characterized as being two aryl groups linked by a spacer. Relatively speaking, the structure of the linked diaryl compounds is much simpler than previously reported HIV-1 reverse transcriptase inhibitors. Accordingly, the finding of this activity for the linked diaryl compounds is surprising. In fact, the general class of linked diaryl compounds have most often been described as photographic agents. For example, EP 0436190, U.S. Pat. No. 5,124,230 and U.S. Pat. No. 6,221,573. Only a few publications have reported pharmacodynamic or therapeutic properties for this class. Such references can be summarized as follows:

[0009] U.S. Pat. No. 4,186,131 and U.S. Pat. No. 4,252,815 disclose that certain (phenyltetrazolyloxy)propyl arylamines possess antiarrhythmic and β -adrenergic blocking actions.

[0010] U.S. Pat. No. 4,399,285 relates to substituted tetrazolyloxy-carboxylic acid amides which are stated to be herbicides.

[0011] Kejha et al., *Cesk. Farm.*, 39,294(1990) reported that a series of 1-phenyl-5-thio derivatives exhibited analgesic activity.

[0012] Toth and Simon, *Monatsh. Chem.*, 125(8-9), 977 (1994) report that certain carbamic acid esters linked with tetrazole-5 thiol exhibit pesticidal, herbicidal and antifungal activities.

[0013] U.S. Pat. No. 5,990,126 discloses that certain diarylsulfide derivatives are N-methyl-D-aspartic acid receptor antagonists.

[0014] U.S. Pat. No. 6,245,817 B1 and related WO 98/35955 disclose that α -alkoxyamide and α -thioalkoxyamide compounds are antagonists of the NPY5 receptor, and consequently the compounds are useful for treating obesity related disorders.

[0015] WO 01/16357A2 reports that N-(4-methoxyphenyl)-2-((1-phenyl-1H-tetrazol-5-yl)thio)-acetamide is an inhibitor of sugar alcohol phosphatases with possible application as an antifungal agent.

[0016] EP 0 035 046 B1 and related U.S. Pat. Nos. 4,540,703, 4,663,323 and 4,766,120 describe tetrazole derivatives having a further unsaturated heterocyclic ring; the derivatives are claimed to be antiulcer and antiinflammatory drugs.

[0017] Lagoja et al., *Helv. Chim. Acta*, 85, 1883 (2002) relates to a series of 1,2,4-triazole derivatives which inhibit HIV-1, HIV-2 and SIV replication.

[0018] Also, WO 02/070470 discloses a series of benzophenone bridged triaryl derivatives as HIV reverse transcriptase inhibitors, useful for treating viral infections.

[0019] In addition, a search of the CAS Chemical Registry System (2002) revealed the structures but no utility of a number of N-aryl-2-arylacetamide derivatives. For example, 2-{{1-(1-naphthalenyl)-1H-tetrazol-5-yl}thio}-N-(2-nitrophenyl)acetamide, Registry No.: 310456-59-8; N-(4-bromophenyl)-2-{{1-(3,4-dimethylphenyl)-1H-tetrazol-5-yl}thio}acetamide, Registry No.: 431890-67-4; 2-{{1-(2,4-difluorophenyl)-1H-tetrazol-5-yl}thio}-N-(2,6-dimethylphenyl)acetamide, Registry No.: 335207-29-9; and N-(2,4,6-trimethylphenyl)-2-{{1-(2,4,6-trimethylphenyl)-1H-tetrazol-5-yl}thio}acetamide, Registry No. 385383-12-0.

SUMMARY OF THE INVENTION

[0020] The invention provides a method for treating HIV infection comprising administering to a human infected by HIV, a therapeutically effective amount of a compound of this invention. The compounds are potent inhibitors of wild-type (WT) and double mutant strains of HIV-1 RT, particularly the double mutation K103N/Y181C.

[0021] In a first aspect the invention provides a method for treating HIV infection comprising administering to an infected human a therapeutically effective amount of a compound represented by formula 1:



[0022] wherein Ar^1 is

[0023] (i) 5- or 6-membered aromatic heterocycle containing 1 to 4 heteroatoms selected from N, O or S; said heterocycle optionally substituted with (C_{1-4}) alkyl, (C_{3-7}) cycloalkyl, (C_{5-7}) cycloalkyl- (C_{1-4}) alkyl, wherein said alkyl, cycloalkyl or cycloalkylalkyl may be mono-substituted with $-\text{OH}$; and/or phenyl when the heterocycle contains 1 to 3 N-atoms; in either instance, the said heterocycle is optionally substituted with:

[0024] phenyl, phenylmethyl, 5- or 6-membered aromatic heterocycle, fused phenyl-unsaturated or saturated 5- or 6-membered carbocycle, fused phenyl-{unsaturated or saturated 5- or 6-membered carbocycle}methyl, or fused phenyl-5- or 6-membered aromatic heterocycle; each of said phenyl, phenylmethyl, aromatic heterocycle, fused phenyl-carbocycle, fused phenyl-(carbocycle)methyl or fused phenyl-aromatic heterocycle in turn is substituted optionally with 1 to 3 substituents selected independently from:

[0025] (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{5-7}) cycloalkyl- (C_{1-4}) alkyl, (C_{2-6}) alkenyl, $\text{O}-(\text{C}_{1-4})$ alkyl, $\text{S}-(\text{C}_{1-4})$ alkyl, halo, CF_3 , OCF_3 , OH, NO_2 , CN, phenyl optionally substituted with C_{1-4} alkyl or nitro, phenylmethyl optionally substituted with C_{1-6} alkyl or nitro, SO_2NH_2 , $\text{SO}_2-(\text{C}_{1-4})$ alkyl, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{OR}^1$, NR^2R^3 , morpholino or 1-pyrrolidyl,

[0026] wherein R^1 is H or (C_{1-4}) alkyl, and wherein R^2 and R^3 each independently is H or (C_{1-4}) alkyl; wherein said substituents are sterically compatible; or

[0027] (ii) unsaturated or saturated 5- or 6-membered carbocycle substituted with phenyl or naphthyl, said unsaturated or saturated carbocycle, or the phenyl or

naphthyl optionally substituted with the same 1 to 3 substituents as defined for the substituents in section (i); or

[0028] (iii) benzimidazole optionally N-substituted with phenyl or a fused phenyl-carbocycle as defined above;

[0029] X is a heteroatom selected from O, S, SO, SO^+ or NR^4 wherein R^4 is H or (C_{1-4}) alkyl; or X is a valence bond or $\text{CR}^{\text{AA}}\text{R}^{\text{AB}}$ wherein R^{AA} and R^{AB} each independently is H or (C_{1-4}) alkyl; and

[0030] when X is a heteroatom, including NR^4 :

[0031] W is a divalent radical selected from:

[0032] (a) $(\text{CR}^5\text{R}^6)_{1,2}-\text{C}(\text{Z}^{\text{A}})\text{NR}^6$ wherein R^5 and R^6 each independently is H or (C_{1-4}) alkyl, R^6 is H or (C_{1-4}) alkyl, and Z^{A} is oxo or thioxo;

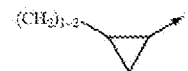
[0033] (b) $\text{D}-\text{C}(\text{Z}^{\text{B}})$ wherein D is (C_{1-4}) alkylene, (C_{1-4}) alkylene-O or (C_{1-4}) alkylene- NR^7 wherein R^7 is H or (C_{1-4}) alkyl, and Z^{B} is oxo or thioxo;

[0034] (c) $\text{CH}_2\text{C}(\text{Z}^{\text{C}})\text{NR}^7\text{A}-(\text{C}_{1-4})$ alkylene wherein Z^{C} is oxo or thioxo and R^7A is H or (C_{1-4}) alkyl;

[0035] (d) (C_{1-4}) alkylene- $\text{NR}^7\text{B}\text{C}(\text{Z}^{\text{D}})\text{NR}^7\text{C}$ wherein R^7B and R^7C each independently is H or (C_{1-4}) alkyl, and Z^{D} is oxo or thioxo;

[0036] (e) (C_{1-4}) alkylene optionally substituted with OH, or optionally disubstituted with OH when the (C_{1-4}) alkylene contains 2 to 4 carbon atoms; (C_{2-4}) alkenyl optionally substituted with halo; or

[0037] cis- or trans-



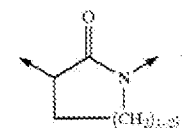
[0038] or

[0039] (f) $\{(C_{1-4})\text{alkylene}\}-\text{O}$ optionally substituted on the alkylene portion with OH;

[0040] (g) $\{(C_{1-4})\text{alkylene}\}-\text{NR}^8$ optionally substituted on the alkylene portion with OH, and R^8 is H or (C_{1-4}) alkyl;

[0041] (h) $(C_{1-4})\text{alkylene}-\text{C}(\text{Z}^{\text{E}})(C_{1-4})\text{alkylene}$ wherein Z is oxo or thioxo; or

[0042] (i)



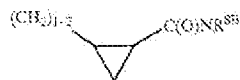
[0043] or

[0044] (j) $(\text{CR}^5\text{R}^6)_{1,2}-\text{NR}^9-(\text{CR}^5\text{R}^6)_{1,2}$ wherein R^5 and R^6 each independently is H or (C_{1-4}) alkyl, R^9 is H or (C_{1-4}) alkyl; or

[0045] when X is a valence bond:

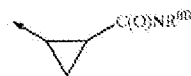
[0046] W is a $\{(C_{2-4})\text{alkenyl}\}C(O)NR^{8A}$,

[0047] cis- or trans-



[0048] or

[0049] cis- or trans-



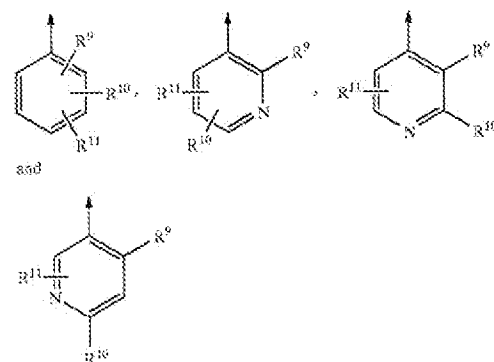
[0050] wherein R^{8A} and R^{8B} each is H or $(C_{1-4})\text{alkyl}$; or

[0051] when X is $CR^{8A}R^{8B}$ as defined above:

[0052] W is selected from $\{(C_{1-4})\text{alkylene}\}C(O)NR^{9C}$, $S-\{(C_{1-4})\text{alkylene}\}C(O)NR^{9B}$, $O-\{(C_{1-4})\text{alkylene}\}C(O)NR^{9B}$, or $NR^{9E}-\{(C_{1-4})\text{alkylene}\}-NR^{9G}$, wherein R^{9C} , R^{9D} , R^{9E} , R^{9F} and R^{9G} each independently is H or $(C_{1-4})\text{alkyl}$; and

[0053] Ar^2 is

[0054] (i) a phenyl or pyridinyl selected from the formulas



[0055] wherein R^9 , R^{10} and R^{11} each independently represents:

[0056] H, $(C_{1-6})\text{alkyl}$, $(C_{3-7})\text{cycloalkyl}$, $(C_{3-7})\text{cycloalkyl}-(C_{1-3})\text{alkyl}$, $(C_{2-4})\text{alkenyl}$, $O-(C_{1-4})\text{alkyl}$, $S-(C_{1-4})\text{alkyl}$, halo, CF_3 , OCF_3 , OH, NO_2 , CN , $-NR^{N1}R^{N2}$, $-C(O)R^{21}$, $-(C_{1-3})\text{alkyl}-C(O)R^{21}$, $-C(O)OR^{22}$, $-(C_{1-3})\text{alkyl}-C(O)OR^{22}$, $-SO_2-(C_{1-3})\text{alkyl}-C(O)OR^{22}$, wherein R^{21} is $(C_{1-4})\text{alkyl}$ and R^{22} is H or $(C_{1-4})\text{alkyl}$; $C(O)NH_2$, $-C(O)NH_2$,

[0057] $S(O)-(C_{1-4})\text{alkyl}$, $SO_2-(C_{1-4})\text{alkyl}$, SO_2NH_2 ,

[0058] phenyl, phenylmethyl, phenyl- SO_2 -, 2-, 3- or 4-pyridinyl, 1-pyrrolyl, whereby said phenyl, pyridinyl and pyrrolyl may have one or more substituents selected from the group consisting of halo, NO_2 , $C_{1-3}\text{-alkyl}$ and CF_3 ;

[0059] wherein the substituents R^9 , R^{10} and R^{11} are sterically compatible;

[0060] wherein R^{N1} , R^{N2} each independently represent H or $(C_{1-6})\text{alkyl}$, whereby R^{N1} and R^{N2} may be covalently bonded to each other to form together with the N-atom to which they are attached to a 4 to 7-membered heterocycle whereby the $-CH_2-$ group at the position 4 of a 6 or 7-membered heterocycle may be replaced by $-O-$, $-S-$ or $-NR^{N3}-$ wherein R^{N3} represents H, $-C(O)OR^{22}$, $(C_{1-6})\text{alkyl}$, $(C_{3-7})\text{cycloalkyl}$ or $(C_{3-7})\text{cycloalkyl}-(C_{1-3})\text{alkyl}$, wherein R^{22} is H or $(C_{1-4})\text{alkyl}$; or

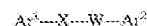
[0061] (ii) Ar^2 is a fused phenyl-(saturated or unsaturated 5- or 6-membered carbocyclic ring optionally substituted with 1 to 3 substituents selected independently from $(C_{1-4})\text{alkyl}$, $O-(C_{1-4})\text{alkyl}$, $S-(C_{1-4})\text{alkyl}$, NO_2 or halo; or

[0062] (iii) Ar^2 is a 5- or 6-membered aromatic heterocycle containing 1 to 4 heteroatoms selected from N, O or S, or a fused phenyl-5- or 6-membered heterocycle, said aromatic heterocycle or fused phenyl-heterocycle is optionally substituted with 1 to 3 substituents selected independently from $(C_{1-4})\text{alkyl}$, $O-(C_{1-4})\text{alkyl}$, $S-(C_{1-4})\text{alkyl}$, NO_2 or halo; or

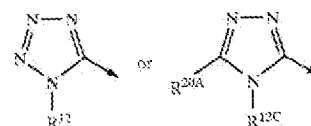
[0063] (iv) Ar^2 is phthalimido and W is $(C_{1-4})\text{alkylene}$;

[0064] or a pharmaceutically acceptable salt, ester or pro-drug thereof.

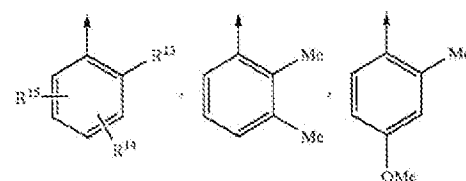
[0065] Furthermore, a second aspect of this invention provides compounds of formula 1:



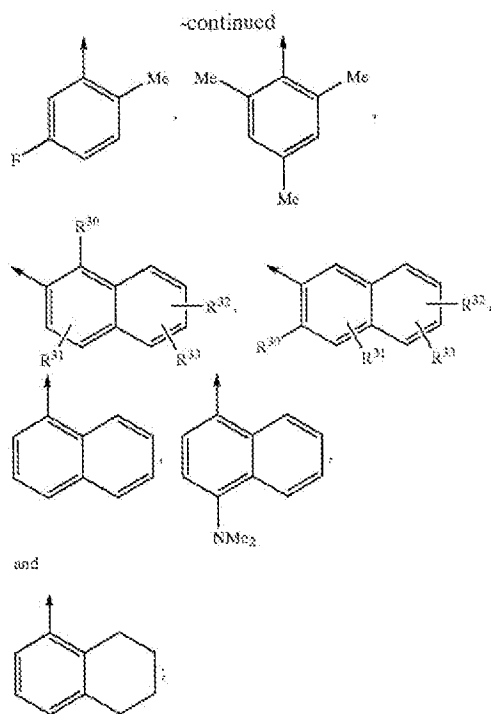
[0066] wherein Ar^1 is



[0067] wherein R^{12} is selected from the group consisting of



Mar. 10, 2005



[0068] R^{13} represents Cl, Br, $\text{COO}(\text{C}_{1-4})\text{alkyl}$ and

[0069] if R^9 is NO_2 , Cl or Br, then R^{13} may also represent F or CH_3 ;

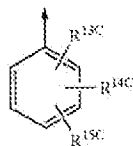
[0070] R^{14} , R^{15} ,

[0071] R^{31} , R^{32} ,

[0072] R^{33} are each independently selected from the group consisting of H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}-(\text{C}_{1-3})\text{alkyl}$, $(\text{C}_{2-6})\text{alkenyl}$, $\text{O}-(\text{C}_{1-4})\text{alkyl}$, $\text{S}-(\text{C}_{1-4})\text{alkyl}$, halo, CF_3 , OCF_3 , OH, NO_2 , CN, SO_2NH_2 , $\text{SO}_2-(\text{C}_{1-4})\text{alkyl}$, $\text{C}(\text{O})\text{OR}^1$ wherein R^1 is H or $(\text{C}_{1-4})\text{alkyl}$, or NR^2R^3 wherein R^2 and R^3 each independently is H or $(\text{C}_{1-4})\text{alkyl}$;

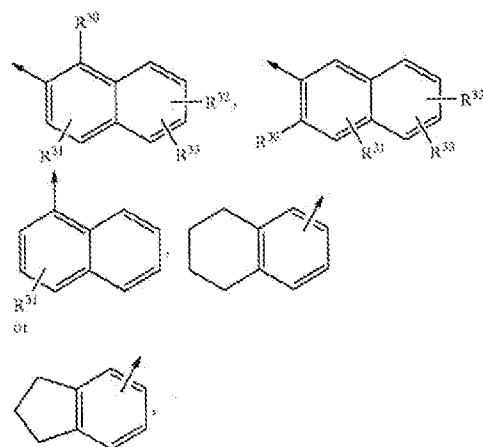
[0073] R^{30} represents H, Cl, Br, $\text{COO}(\text{C}_{1-4})\text{alkyl}$;

[0074] R^{12C} is a phenyl of formula



[0075] wherein R^{13C} , R^{14C} and R^{15C} each independently represents H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}-(\text{C}_{1-3})\text{alkyl}$, $(\text{C}_{2-6})\text{alkenyl}$, $\text{O}-(\text{C}_{1-4})\text{alkyl}$, $\text{S}-(\text{C}_{1-4})\text{alkyl}$, halo, CF_3 , OCF_3 , OH, NO_2 , CN, SO_2NH_2 , $\text{SO}_2-(\text{C}_{1-4})\text{alkyl}$, $\text{C}(\text{O})\text{OR}^1$ wherein R^1 is H or $(\text{C}_{1-4})\text{alkyl}$, or NR^2R^3 wherein R^2 and R^3

each independently is H or $(\text{C}_{1-4})\text{alkyl}$; provided that at least one of R^{13C} , R^{14C} and R^{15C} is other than hydrogen; or R^{12C} is



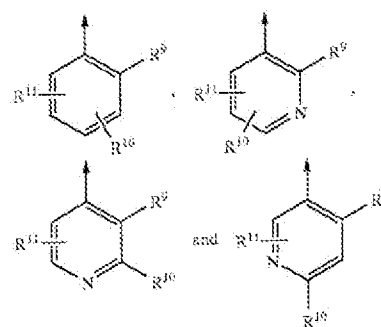
[0076] wherein R^{30} , R^{31} , R^{32} , R^{33} are as defined hereinbefore; and

[0077] R^{20A} is H, $(\text{C}_{1-4})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$ or $(\text{C}_{3-7})\text{cycloalkyl}-(\text{C}_{1-3})\text{alkyl}$, wherein said alkyl, cycloalkyl or cycloalkylalkyl may be monosubstituted with $-\text{OH}$; and

[0078] X is S or O;

[0079] W is $\text{CH}_2\text{C}(\text{O})\text{NR}^6$ wherein R^6 is H or $(\text{C}_{1-4})\text{alkyl}$; and

[0080] Ar^2 is selected from the group consisting of



[0081] wherein R^9 is halo or NO_2 ; and if R^{13} is Cl or Br, then R^9 may also represent $(\text{C}_{1-3})\text{alkyl}$;

[0082] R^{10} , R^{11} are independently of each other selected from the group consisting of H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}-(\text{C}_{1-3})\text{alkyl}$, $(\text{C}_{2-6})\text{alkenyl}$, $\text{O}(\text{C}_{1-6})\text{alkyl}$, $\text{S}(\text{C}_{1-6})\text{alkyl}$, halo, CF_3 , OCF_3 , OH, NO_2 , CN, $-\text{NR}^{21}\text{R}^{22}$, $-\text{C}(\text{O})\text{R}^{21}$, $-(\text{C}_{1-3})\text{alkyl}-\text{C}(\text{O})\text{R}^{21}$, $-\text{C}(\text{O})\text{OR}^{22}$, $-(\text{C}_{1-3})\text{alkyl}-\text{C}(\text{O})\text{OR}^{22}$, $-\text{SO}_2-(\text{C}_{1-3})\text{alkyl}-\text{C}(\text{O})\text{OR}^{22}$, wherein R^{21} is $(\text{C}_{1-4})\text{alkyl}$ and R^{22} is H or $(\text{C}_{1-4})\text{alkyl}$;

a)alkyl ; $-(\text{C}_{1-4})\text{alkyl}-\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NH}_2$, $\text{S}(\text{O})-(\text{C}_{1-6})\text{alkyl}$, $-\text{SO}_2-(\text{C}_{1-6})\text{alkyl}$, $-\text{SO}_2\text{-phenyl}$, $-\text{SO}_2-\text{NH}_2$, phenyl, phenylmethyl, 2-, 3- or 4-pyridinyl, 1-pyrrolyl, whereby said phenyl, pyridinyl and pyrrolyl may have one or more substituents selected from the group consisting of halo, NO_2 , $\text{C}_{1-3}\text{-alkyl}$ and CF_3 ;

[0083] or a pharmaceutically acceptable salt, ester or prodrug thereof.

[0084] According to another aspect of the invention, there is provided the use of a compound of formula 1 as defined hereinbefore and hereinafter, or a pharmaceutically acceptable salt, ester or prodrug thereof, for the manufacture of a medicament for the treatment or prevention of an HIV infection

[0085] According to yet another aspect of the invention, there is provided the use of a compound of formula 1 as defined hereinbefore and hereinafter, or a pharmaceutically acceptable salt, ester or prodrug thereof, in combination with one or more other antiretroviral drugs.

[0086] According to a further aspect of the invention, there is provided a pharmaceutical composition, comprising a compound of formula 1 as defined hereinbefore and hereinafter, or a pharmaceutically acceptable salt, ester or prodrug thereof, and optionally one or more pharmaceutically acceptable carriers.

[0087] According to another aspect of the invention, there is provided a pharmaceutical composition for the treatment or prevention of HIV infection, comprising a compound of formula 1 as defined hereinbefore and hereinafter, or a pharmaceutically acceptable salt, ester or prodrug thereof, and optionally one or more pharmaceutically acceptable carriers.

[0088] According to a sixth aspect of the invention, there is provided a process for preparing a compound of formula 1 wherein Ar^1 and Ar^2 are as defined hereinbefore and hereinafter, X is S or O and W is $(\text{CR}^5\text{R}^{5A})_{1-2}\text{C}(\text{O})\text{NR}^6$, wherein R^5 , R^{5A} and R^6 each independently is H or $(\text{C}_{1-4})\text{alkyl}$, comprising:

[0089] a) reacting a thiol or alcohol of formula $\text{Ar}^1-\text{X}-\text{H}$ with an ω -halo alkanolic alkyl ester of formula $\text{Y}-(\text{CR}^5\text{R}^{5A})_{1-2}\text{C}(\text{O})\text{OR}^A$ wherein Y is halo and R^A is $(\text{C}_{1-4})\text{alkyl}$, in the presence of a base, to obtain the corresponding ester of formula $\text{Ar}^1-\text{X}-(\text{CR}^5\text{R}^{5A})_{1-2}\text{C}(\text{O})\text{OR}^A$, followed by hydrolysis of the ester to the corresponding acid wherein $\text{R}^A=\text{H}$, and coupling the latter acid with an aromatic amine of general formula HNR^6-Ar^2 in the presence of a coupling agent to obtain the corresponding compound of formula 1 wherein Ar^1 , Ar^2 , X and W are as defined herein; or

[0090] b) reacting a thiol or alcohol of formula $\text{Ar}^1-\text{X}-\text{H}$ wherein Ar^1 and X are as defined herein with an anilide of formula $\text{Y}-(\text{CR}^5\text{R}^{5A})_{1-2}\text{C}(\text{O})\text{NR}^6-\text{Ar}^2$ wherein Y, R^5 , R^{5A} , R^6 and Ar^2 are as defined herein, in the presence of a base to obtain the corresponding compound of formula 1.

DETAILED DESCRIPTION OF THE INVENTION

[0091] Definitions

[0092] The following definitions apply unless otherwise noted:

[0093] As used herein, the term " $(\text{C}_{1-4})\text{alkyl}$ ", either alone or in combination with another radical, is intended to mean acyclic straight or branched chain alkyl radicals containing from one to four carbon atoms respectively. Examples of such radicals include methyl (Me), ethyl (Et), propyl (Pr), 1-methylethyl (iPr), butyl (Bu), 2-methylpropyl (tBu), and 1,1-dimethylethyl (tBu), wherein the abbreviations commonly used herein are given in brackets.

[0094] As used herein, the term " $\text{O}-(\text{C}_{1-4})\text{alkyl}$ ", either alone or in combination with another radical, refers to alkoxy radicals containing for one to four carbon atoms and includes methoxy (OMe), ethoxy (OEt), propoxy (OPr), 1-methylethoxy (OiPr), butoxy (OBu) and 1,1-dimethylethoxy (OtBu), wherein the abbreviations commonly used herein are given in brackets.

[0095] As used herein, the term " $\text{S}-(\text{C}_{1-4})\text{alkyl}$ ", either alone or in combination with another radical, refers to alkylthio, radicals containing one to four carbon atoms and includes methylthio, ethylthio, propylthio, (1-methylethyl)thio, butylthio and (1,1-dimethylethyl)thio.

[0096] As used herein, the term "halo" means a halo radical selected from bromo, chloro, fluoro or iodo.

[0097] As used herein, the term " $(\text{C}_{1-4})\text{alkylene}$ ", either alone or in combination with another radical, means a divalent alkyl radical derived by removal of two hydrogens atoms from an aliphatic hydrocarbon containing one to four carbon atoms and includes $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{Me})-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ and $-\text{CH}_2\text{CH}(\text{Me})\text{CH}_2-$.

[0098] As used herein, the term " $(\text{C}_{2-4})\text{alkenyl}$ ", either alone or used with another radical, means a divalent alkene radical derived by removal of two hydrogen atoms from an olefinic hydrocarbon containing two to four carbon atoms and includes $-\text{CH}=\text{CH}-$, $-\text{CH}_2\text{CH}=\text{CH}-$, $-\text{CH}_2\text{CH}=\text{CHCH}_2-$ and $-\text{CH}(\text{Me})\text{CH}=\text{CH}-$. The cis and trans isomers, and mixtures thereof, of the $(\text{C}_{2-4})\text{alkenyl}$ radical can be encompassed by the term.

[0099] As used herein, the term "unsaturated or saturated 5- or 6-membered carbocycle", either alone or in combination with another radical, means a unsaturated or saturated monocyclic hydrocarbon containing 5 to 6 carbon atoms and includes, for example, phenyl, 1-cyclohexenyl, 1,3-cyclohexadienyl, cyclohexenyl, 1-cyclopentenyl and cyclopentenyl. In the following Ph is used as an abbreviation for phenyl.

[0100] As used herein, the term "fused phenyl-(saturated or unsaturated 5- or 6-membered carbocycle)" or "fused phenyl-carbocycle", either alone or in combination with another radical, means a phenyl that is fused with a saturated or unsaturated 5- or 6-membered carbocyclic ring. Examples include naphthalenyl, 1, 2, 3, 4-tetrahydronaphthalenyl, 2, 3-dihydro-1H-indenyl and indenyl.

[0101] As used herein, the term "aromatic heterocycle", either alone or in combination with another radical, means a monovalent radical derived by removal of a hydrogen from

a 5- or 6-membered aromatic heterocycle containing, 1 to 4 heteroatoms selected from N, O and S. Examples of suitable aromatic heterocycles include tetrazolyl, pyridinyl, imidazolyl, 1,2,4-triazolyl, isoxazolyl and thiazolyl.

[0102] As used herein, the term "heterocycle", either alone or in combination with another radical, is intended to mean a monovalent radical derived by removal of a hydrogen from a 5- or 6-membered saturated or unsaturated (including aromatic) heterocycle containing 1 to 4 heteroatoms selected from N, O and S. Examples of suitable heterocycles include 1,3-dioxolanyl, pyrrolidinyl, pyrazolyl and thiazolyl.

[0103] As used herein, the term "fused phenyl-5- or 6-membered aromatic heterocycle", either alone or in combination with another radical, is intended to mean a phenyl that is fused with a 5- or 6-membered aromatic heterocycle having 1 to 2 nitrogen atoms. Examples include 1H-benzimidazolyl, quinolinyl and isoquinolinyl.

[0104] As used herein, the term "inhibitor of HIV replication" refers to an agent capable of substantially reducing or essentially eliminating the ability of HIV-1 reverse transcriptase to replicate a DNA copy from an RNA template.

[0105] As used herein, the term "single or double mutant strains" means that either one or two amino acid residues that are present in WT HIV-1 strain have been replaced by residues not found in the WT strain. For example, the single mutant Y181C is prepared by site-directed mutagenesis in which the tyrosine at residue 181 has been replaced by a cysteine residue. Similarly, for the double mutant K103N/Y181C, an asparagine residue has replaced the lysine at residue 103 and a cysteine residue has replaced the tyrosine at residue 181.

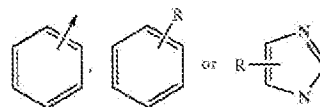
[0106] As used herein, the term "pharmaceutically acceptable salt" means a salt of a compound which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. Where applicable and compatible with the chemical properties of the compound of formula 1, the term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts. Lists of suitable salts are found in, e.g., S. M. Birge et al., *J. Pharm. Sci.*, 1977, 66, pp. 1-19, which is hereby incorporated by reference in its entirety.

[0107] The term "pharmaceutically-acceptable acid addition salt" means those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, nitric acid, phosphoric acid, and the like, and organic acids such as acetic acid, trichloroacetic acid, trifluoroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 2-acetoxybenzoic acid, butyric acid, camphoric acid, camphorsulfonic acid, cinnamic acid, citric acid, digluconic acid, ethanesulfonic acid, glutamic acid, glycolic acid, glycerophosphoric acid, hemisulfic acid, heptanoic acid, hexanoic acid, formic acid, fumaric acid, 2-hydroxyethanesulfonic acid (isethionic acid), lactic acid, maleic acid, hydroxymaleic acid, malic acid, malonic acid,

mandelic acid, mesitylenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid, nicotinic acid, 2-naphthalenesulfonic acid, oxalic acid, pantoic acid, pectinic acid, phenylacetic acid, 3-phenylpropionic acid, picric acid, pivalic acid, propionic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, sulfanilic acid, tartaric acid, p-toluenesulfonic acid, undecanoic acid, and the like.

[0108] The term "pharmaceutically-acceptable base addition salt" means those salts which retain the biological effectiveness and properties of the free acids and which are not biologically or otherwise undesirable, formed with inorganic bases such as ammonia or hydroxide, carbonate, or bicarbonate of ammonium or a metal cation such as sodium, potassium, lithium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically-acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, quaternary amine compounds, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins, such as methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tetramethylammonium compounds, tetraethylammonium compounds, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, dibenzylamine, N,N-dibenzylphenethylamine, 1-phenamine, N,N'-dibenzylethylenediamine, polyamine resins, and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

[0109] When a valence bond on a phenyl ring or heterocyclic ring is illustrated as follows:



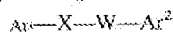
[0110] then the indication is that the valence bond can replace any hydrogen atom on the ring.

[0111] As used herein, the term "prodrug" refers to pharmacologically acceptable derivatives, such that the resulting biotransformation product of the derivative is the active drug, as defined in compounds of formula 1: Examples of such derivatives include, but are not limited to, esters and amides (see Goodman and Gilman in *The Pharmacological Basis of Therapeutics*, 9th ed., McGraw-Hill, Int. Ed. 1995, "Biotransformation of Drugs," p 11-16, incorporated herein by reference).

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0112] According to a first embodiment of the first aspect of the present invention there is provided a method for

treating HIV infection comprising administering to an infected human a therapeutically effective amount of a compound represented by formula 1:



[0113] wherein Ar^1 is

[0114] (i) 5- or 6-membered aromatic heterocycle containing 1 to 4 heteroatoms selected from N, O or S; said heterocycle optionally substituted with (C_{1-4}) alkyl or phenyl when the heterocycle contains 1 to 3 N-atoms; in either instance, the said heterocycle is optionally substituted with:

[0115] phenyl, phenylmethyl, 5- or 6-membered aromatic heterocycle, fused phenyl-unsaturated or saturated 5- or 6-membered carbocycle, fused phenyl-unsaturated or saturated 5- or 6-membered carbocycle}methyl, or fused phenyl-5- or 6-membered aromatic heterocycle; each of said phenyl, carbocycle or heterocycle, in turn is substituted optionally with 1 to 3 substituents selected independently from:

[0116] (C_{1-4}) alkyl, $\text{O---}(\text{C}_{1-4})$ alkyl, $\text{S---}(\text{C}_{1-4})$ alkyl, halo, CF_3 , OH, NO_2 , CN, phenyl optionally substituted with (C_{1-4}) alkyl, SO_2NH_2 , $\text{SO}_2\text{---}(\text{C}_{1-4})$ alkyl, C(O)OR^1 wherein R^1 is H or (C_{1-4}) alkyl, or NR^2R^3 wherein R^2 and R^3 each independently is H or (C_{1-4}) alkyl; wherein said substituents are sterically compatible; or

[0117] (ii) unsaturated or saturated 5- or 6-membered carbocycle substituted with phenyl or naphthyl, said unsaturated or saturated carbocycle, or the phenyl or naphthyl optionally substituted with the same 1 to 3 substituents as defined for the substituents in section (i); or

[0118] (iii) benzimidazole optionally N-substituted with phenyl or a fused phenyl-carbocycle as defined above;

[0119] X is a heteroatom selected from O, S or NR^4 wherein R^4 is H or (C_{1-4}) alkyl; or X is a valence bond or $\text{CR}^{4A}\text{R}^{4B}$ wherein R^{4A} and R^{4B} each independently is H or (C_{1-4}) alkyl; and

[0120] when X is a heteroatom:

[0121] W is a divalent radical selected from:

[0122] (a) $(\text{CR}^5\text{R}^{5A})_{1-2}\text{---C(Z}^A)\text{NR}^6$ wherein R^5 and R^{5A} each independently is H or (C_{1-4}) alkyl, R^6 is H or (C_{1-4}) alkyl, and Z^A is oxo or thioxo;

[0123] (b) $\text{D---C(Z}^B)$ wherein D is (C_{1-4}) alkylene, (C_{1-4}) alkylene-O or (C_{1-4}) alkylene- NR^7 wherein R^7 is H or (C_{1-4}) alkyl, and Z^B is oxo or thioxo;

[0124] (c) $\text{CH}_2\text{C(Z}^C)\text{NR}^{7A}\text{---}(\text{C}_{1-4})$ alkylene wherein Z^C is oxo or thioxo and R^{7A} is H or (C_{1-4}) alkyl;

[0125] (d) (C_{1-4}) alkylene- $\text{NR}^{7B}\text{C(Z}^D)\text{NR}^{7C}$ wherein R^{7B} and R^{7C} each independently is H or (C_{1-4}) alkyl, and Z^D is oxo or thioxo;

[0126] (e) (C_{1-4}) alkylene optionally substituted with OH, or optionally disubstituted with OH when the (C_{1-4}) alkylene contains 2 to 4 carbon atoms; (C_{2-4}) alkenyl optionally substituted with halo; or

[0127] cis- or trans-



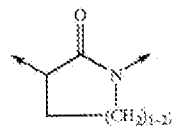
[0128] or

[0129] (f) $\{(\text{C}_{1-4})\text{alkylene}\}\text{---O}$ optionally substituted on the alkylene portion with OH;

[0130] (g) $\{(\text{C}_{1-4})\text{alkylene}\}\text{---NR}^8$ optionally substituted on the alkylene portion with OH, and R^8 is H or (C_{1-4}) alkyl;

[0131] (h) $(\text{C}_{1-4})\text{alkylene---C(Z}^E)(\text{C}_{1-4})\text{alkylene}$ wherein Z^E is oxo or thioxo; or

[0132] (i)



[0133] or

[0134] when X is a valence bond:

[0135] W is a $\{(\text{C}_{2-4})\text{alkenyl}\}\text{C(O)NR}^{8A}$,

[0136] cis- or trans-



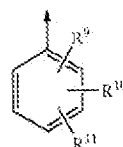
[0137] wherein R^{8A} and R^{8B} each is H or (C_{1-4}) alkyl; or

[0138] when X is $\text{CR}^{4A}\text{R}^{4B}$ as defined above;

[0139] W is selected from $\{(\text{C}_{1-4})\text{alkylene}\}\text{C(O)NR}^{8C}$, $\text{S---}\{(\text{C}_{1-4})\text{alkylene}\}\text{C(O)NR}^{8D}$, $\text{O---}\{(\text{C}_{1-4})\text{alkylene}\}\text{C(O)NR}^{8E}$, or $\text{NR}^{8F}\text{---}\{(\text{C}_{1-4})\text{alkylene}\}\text{---NR}^{8G}$ wherein R^{8C} , R^{8D} , R^{8E} , R^{8F} and R^{8G} each independently is H or (C_{1-4}) alkyl; and

[0140] Ar^2 is

[0141] (i) a phenyl of formula



[0142] wherein R^9 , R^{10} and R^{11} each independently represents:

[0143] H, (C_{1-4}) alkyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, halo, CF_3 , OH, NO_2 , phenyl, phenylmethyl, (2-nitrophenyl)methyl, 2-methylphenyl, $-C(O)-(C_{1-4})$ alkyl, $C(O)NH_2$, $S(O)-(C_{1-4})$ alkyl, SO_2NH_2 , 2-, 3- or 4-pyridinyl, morpholino or 1-pyrrolyl, or $-C(O)OR^{22}$, wherein R^{22} is H or (C_{1-4}) alkyl; wherein the substituents R^9 , R^{10} and R^{11} are sterically compatible; or

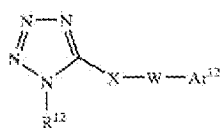
[0144] (ii) Ar^2 is a fused phenyl-saturated or unsaturated 5- or 6-membered carbocyclic ring optionally substituted with 1 to 3 substituents selected independently from (C_{1-4}) alkyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, NO_2 or halo; or

[0145] (iii) Ar^2 is a 5- or 6-membered aromatic heterocycle containing 1 to 4 heteroatoms selected from N, O or S, or a fused phenyl-5- or 6-membered heterocycle, said aromatic heterocycle or fused phenyl-heterocycle is optionally substituted with 1 to 3 substituents selected independently from (C_{1-4}) alkyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, NO_2 or halo; or

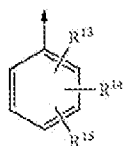
[0146] (iv) Ar^2 is phthalimido and W is (C_{1-4}) alkylene;

[0147] or a pharmaceutically acceptable salt, ester or prodrug thereof.

[0148] According to said first embodiment the method of this invention preferably relates to a compound represented by formula 1a:

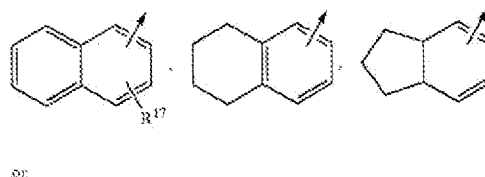


[0149] wherein X, W and Ar^{12} are as defined above and R^{12} is a phenyl of formula

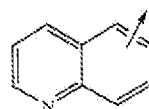


[0150] wherein R^{13} , R^{14} and R^{15} each independently represents H, (C_{1-4}) alkyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, halo, CF_3 , OH, NO_2 , CN, Ph, 2-methylphenyl, SO_2NH_2 , $SO_2-(C_{1-4})$ alkyl, $C(O)NH_2$, morpholino, 1-pyrrolyl, (2- NO_2 Ph) CH_2 , $PhCH_2$, $C(O)OR^{16}$ wherein R^{16} is H or (C_{1-4}) alkyl; or

[0151] R^{12} is



or

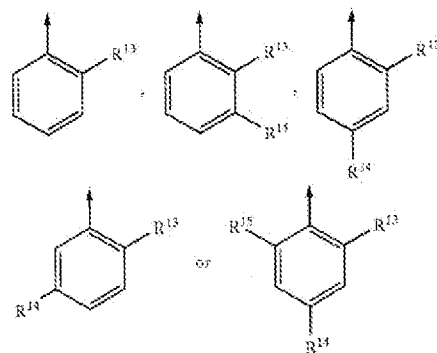


[0152] wherein R^{17} is H, (C_{1-4}) alkyl, $O-(C_{1-4})$ alkyl, halo, CF_3 or $NR^{18}R^{19}$ wherein R^{18} and R^{19} each independently is H or (C_{1-4}) alkyl.

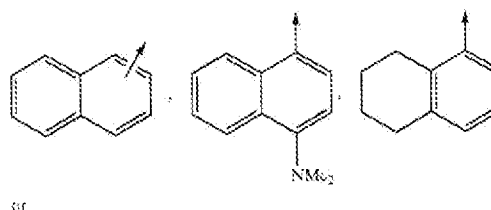
[0153] Most preferably R^{13} , R^{14} and R^{15} each independently represents H, Me, Et, Pr, iPr, tBu, OMe, OEt, OiPr, SMe, SEt, Br, Cl, F, CF_3 , OCF_3 , NO_2 , $C(O)OH$, $C(O)OMe$ or $C(O)OEt$, provided that at least one of R^{13} , R^{14} and R^{15} is other than hydrogen.

[0154] Furthermore, most preferably R^{17} is selected from H, Me, OMe, Cl, F, CF_3 , NH_2 , $NHMe$ or NMe_2 .

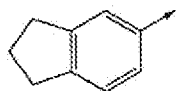
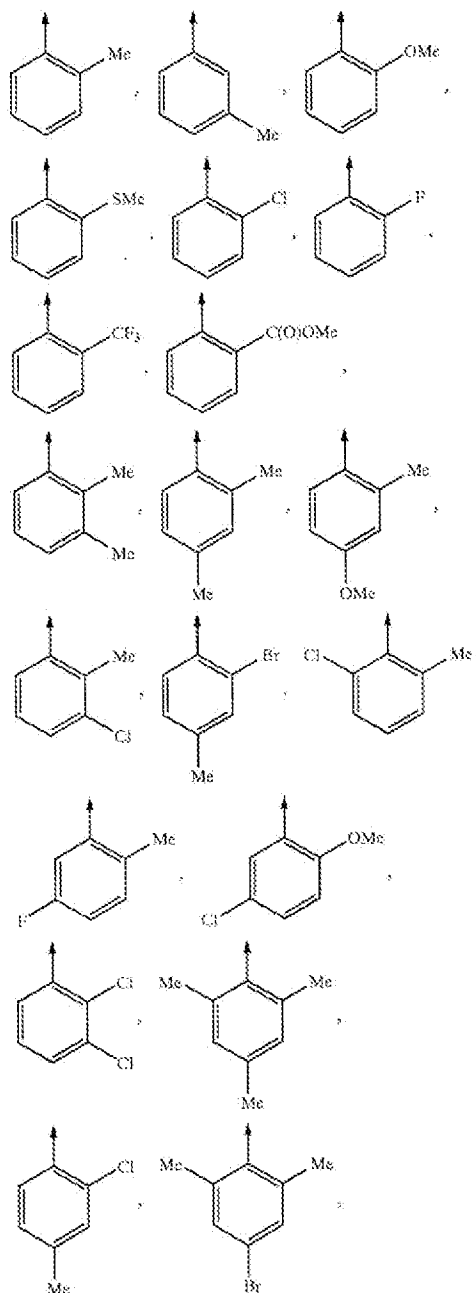
[0155] Regarding the method of said first embodiment, those compounds of formula 1a are more preferred wherein R^{12} is selected from:



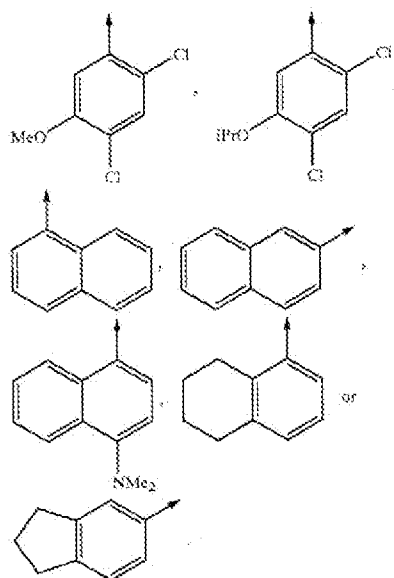
[0156] wherein R^{13} , R^{14} and R^{15} each independently is Me, Et, OMe, O-iPr, SMe, Br, Cl, F, CF_3 or $C(O)OMe$; or wherein R^{12} is selected from:



-continued

[0157] Very most preferably R^{12} is selected from:

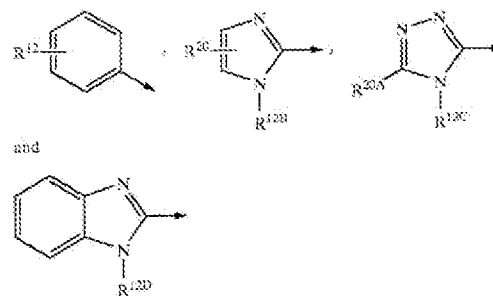
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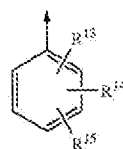
[0158] According to the first embodiment of the first aspect of this invention, alternatively the compound to be administered is preferably a compound represented by formula 1 b:



[0159] wherein X, W and Ar^2 are as defined hereinbefore and Ar^3 is selected from the group consisting of:

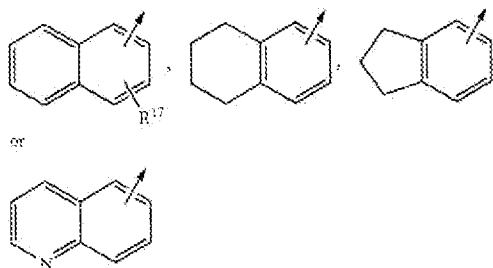


[0160] wherein R^{12A} , R^{12B} , R^{12C} and R^{12D} each is a phenyl of formula



[0161] wherein R^{13} , R^{14} and R^{15} each independently represents H, (C_{1-4}) alkyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, halo,

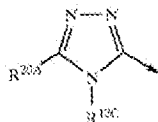
CF₃, OH, NO₂, CN, Ph, 2-methylphenyl, SO₂NH₂, SO₂—(C₁₋₄)alkyl, C(O)NH₂, morpholino, 1-pyrrolyl, (2-NO₂-Ph)CH₂, PhCH₂, C(O)OR¹² wherein R¹² is H or (C₁₋₄)alkyl; or R^{12A}, R^{12B}, R^{12C} and R^{12D} each is



[0162] wherein R¹⁷ is H, (C₁₋₄)alkyl, O—(C₁₋₄)alkyl, halo, CF₃ or NR¹⁸R¹⁹ wherein R¹⁸ and R¹⁹ each independently is H or (C₁₋₄)alkyl;

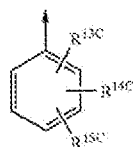
[0163] and R²⁰ and R^{20A} each is H or (C₁₋₄)alkyl.

[0164] Preferably Ar³ is represented by the formula:

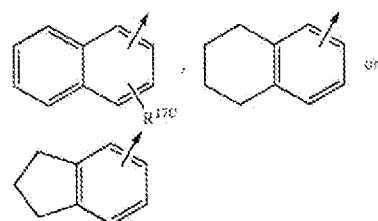


[0165] wherein R^{12C} is as hereinbefore and R^{20A} is H, Me, Et, Pr or iPr.

[0166] Most preferably R^{12C} is a phenyl of the formula



[0167] wherein R^{13C}, R^{14C} and R^{15C} each independently is H, Me, Et, Pr, iPr, OMe, OEt, SMe, SEt, Br, Cl, F, CF₃, NO₂, C(O)OH, C(OMe) or C(O)OEt, provided that at least one of R^{13C}, R^{14C}, and R^{15C} is other than hydrogen, and R^{20A} is H, Me or Et; or R^{12C} is



[0168] wherein R^{17C} is selected from H, Me, OMe, Cl, F, CF₃, NH₂, NHMe or NMe₂; and R^{20A} is H, Me or Et.

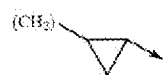
[0169] A method of treatment according to the present invention is preferred wherein the compound is a compound of formula 1 wherein X is O or S, most preferably S.

[0170] Preferably, the method of treatment relates to compounds of formula 1a wherein X is O or S and W is CR⁵R^{5A} C(O)NH wherein R⁵ and R^{5A} each is independently H or Me. More preferably, X is S and W is CH(R⁵)C(O)NH wherein R⁵ is H or Me.

[0171] Preferably, the method of treatment relates to compounds of formula 1a wherein X is O or S and W is D-C(Z^B) wherein D is CH₂CH₂O, CH₂CH₂NH or CH₂CH₂NMe, and Z^B is O. More preferably, X is S and W is CH₂CH₂OC(O).

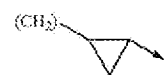
[0172] Preferably, the method of treatment relates to compounds of formula 1a wherein X is O or S and W is CH₂CH₂CH₂, CH₂CH₂CH(OH), CH₂CH(OH)CH₂, trans—CH₂CH=CH, trans—CH₂CF=CH or

[0173] trans-



[0174] More preferably, X is S and W is CH₂CH₂CH(OH), CH₂CH(OH)CH₂ or

[0175] trans-



[0176] Preferably, the method of treatment relates to compounds of formula 1a wherein X is O or S and W is CH₂CH₂O, CH₂CH₂CH₂O, CH₂CH(OH)CH₂O, CH₂CH₂NH, CH(OH)CH₂NH, CH₂CH₂NMe or CH₂CH(OH)CH₂NH. More preferably, X is S and W is CH₂CH(OH)CH₂O, CH(OH)CH₂NH or CH₂CH(OH)CH₂NH.

[0177] Preferably, the method of treatment relates to compounds of formula 1a wherein X is a valence bond and W is CH=CHC(O)NH or

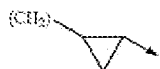


[0178] Preferably, the method of treatment relates to compounds of formula 1a, wherein X is CH₂ and W is SCH₂C(O)NH, OCH₂C(O)NH, NHCH₂C(O)NH or NMeCH₂C(O)NH. More preferably X is CH₂ and W is SCH₂C(O)NH.

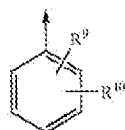
[0179] Most preferably, the method of treatment relates to compounds of formula 1a wherein X is S and W is

$\text{CH}_2\text{C(O)NH}$, CH(Me)C(O)NH , $\text{CH}_2\text{CH}_2\text{CH(OH)}$,
 $\text{CH}_2\text{CH(OH)CH}_2$, $\text{CH}_2\text{CH(OH)CH}_2\text{NH}$ or

[0180] trans-

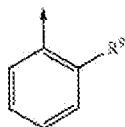


[0181] Preferably, the method of treatment relates to of compounds of formula 1a wherein Ar^2 is phenyl of formula:



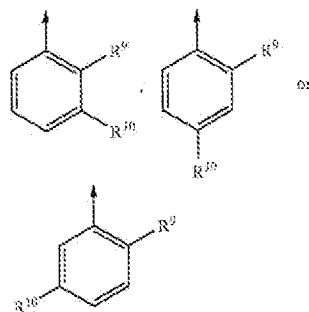
[0182] wherein R^9 and R^{10} each independently represents H, Me, Et, iPr, OMe, OEt, SMe, SEt, Br, Cl, F, I, CF_3 , OH, NO_2 , CN, Ph, C(O)OH , C(O)OMe , C(O)OEt , C(O)Me , C(O)Et , C(O)NH_2 , SO_2Me , SO_2NH_2 , morpholino, 1-pyrrolyl, (2- NO_2Ph) CH_2 or PhCH_2 . More preferably, R^9 is halo or NO_2 , and R^{10} is OMe, halo, OH, NO_2 , Ph, C(O)OH or C(O)OMe .

[0183] More preferably, Ar^2 is selected from



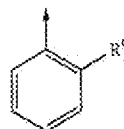
[0184] wherein R^9 is Me, Cl, F, Br, I or NO_2 .

[0185] Even more preferably, Ar^2 is selected from:

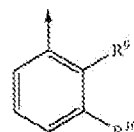


[0186] wherein R^9 is Me, Br, Cl, F, I or NO_2 , and R^{10} is Me, OMe, Cl, F, OH, Ph, C(O)OH , C(O)OMe or CN.

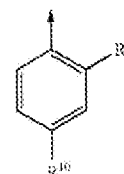
[0187] Most preferably, Ar^2 is selected from:



[0188] wherein R^9 is Cl, Br, I, or NO_2 ; or



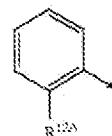
[0189] wherein R^9 and R^{10} each is F; or wherein R^9 and R^{10} each is Cl; or



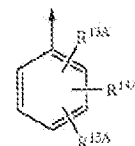
[0190] wherein R^9 is Cl and R^{10} is OMe, Cl, OH, CN, Ph, C(O)OH or C(O)OMe .

[0191] Alternatively, Ar^2 is 5-(1, 2, 3, 4-tetrahydronaphthalenyl).

[0192] In addition, the method of treatment preferably relates to the compounds of formula 1b wherein Ar^3 is

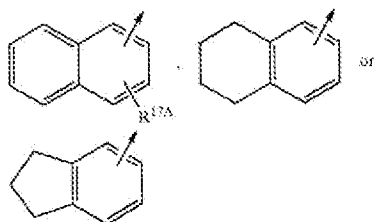


[0193] wherein R^{12A} is as defined hereinabove. More preferably, the use of the compounds of formula 1b wherein Ar^3 is as defined in the last instance and R^{12A} is a phenyl of formula

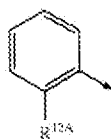


[0194] wherein R^{13A} , R^{14A} , and R^{15A} each independently represents H, Me, Et, Pr, i-Pr, OMe, OEt, SMe, SEt, Br, Cl,

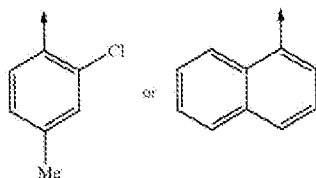
F, CF₃, NO₂, C(O)OH, C(O)OMe or C(O)OEt, provided that at least one of R^{13A}, R^{14A}, and R^{15A} is other than hydrogen; or R^{12A} is



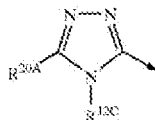
[0195] wherein R^{17A} is selected from H, Me, OMe, Cl, F, CF₃, NH₂, NHMe or NMe₂. Most preferably, the use of the compound of formula 1b wherein Ar³ is



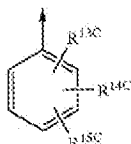
[0196] wherein R^{12A} is



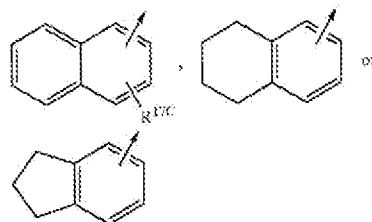
[0197] Preferably, Ar³ is



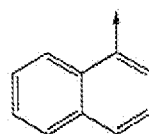
[0198] wherein R^{12C} is as defined in the first instance herein, and R^{20A} is H, Me, Et, Pr or iPr. More preferably, the use of the compounds of formula 1b wherein Ar³ is as defined in the last instance and R^{12C} is a phenyl of formula:



[0199] wherein R^{13C}, R^{14C} and R^{15C} are respectively as defined above for R^{13A}, R^{14A} and R^{15A}; and R^{20A} is H, Me or Et; or R^{12C} is

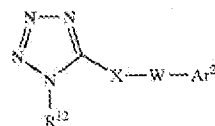


[0200] wherein R^{17C} is selected from H, Me, OMe, Cl, F, CF₃, NH₂, NHMe or NMe₂; and R^{20A} is H, Me or Et. Most preferably, the use of a compound of formula 1b wherein Ar³ is as defined in the last instance and R^{12C} is



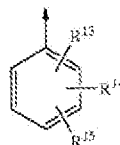
[0201] and R^{20A} is H or Me.

[0202] According to a second embodiment of the first aspect of the present invention there is provided a method for treating HIV infection comprising administering to an infected human a therapeutically effective amount of a compound represented by formula 1a:



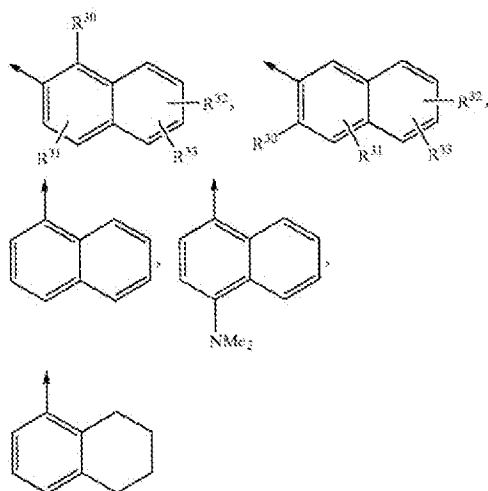
1a

[0203] wherein X, W and Ar² are as defined hereinbefore and R¹² is a phenyl of formula



[0204] wherein R¹³, R¹⁴ and R¹⁵ each independently represents H, (C₁₋₄)alkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₃)alkyl, (C₂₋₆)alkenyl, O-(C₁₋₄)alkyl, S-(C₁₋₄)alkyl, halo, CF₃, OCF₃, OH, NO₂, CN, phenyl, 2-methylphenyl, SO₂NH₂, SO₂-(C₁₋₄)alkyl, C(O)NH₂, morpholino, 1-pyrrolidyl, (2-nitrophenyl)-CH₂, phenylmethyl, C(O)OR¹⁶ wherein R¹⁶ is H or (C₁₋₄)alkyl; or

[0205] wherein R^{12} is selected from the group consisting of

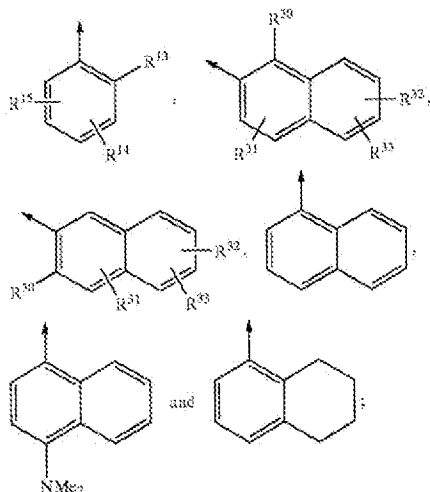


[0206] wherein R^{31} , R^{32} ,

[0207] R^{33} are each independently selected from the group consisting of H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl- (C_{1-3}) alkyl, (C_{2-6}) alkenyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, halo, CF_3 , OCF_3 , OH, NO_2 , CN, SO_2NH_2 , $SO_2-(C_{1-4})$ alkyl, $C(O)OR^1$ wherein R^1 is H or (C_{1-4}) alkyl, or NR^2R^3 wherein R^2 and R^3 each independently is H or (C_{1-4}) alkyl; and

[0208] R^{30} represents H, Cl, Br, $COO(C_{1-4})$ alkyl.

[0209] According to said second embodiment the method of this invention preferably relates to a compound of the formula 1a wherein R^{12} is preferably selected from:



[0210] wherein

[0211] R^{13} represents F, Cl, Br, CH_3 , $COO(C_{1-4})$ alkyl;

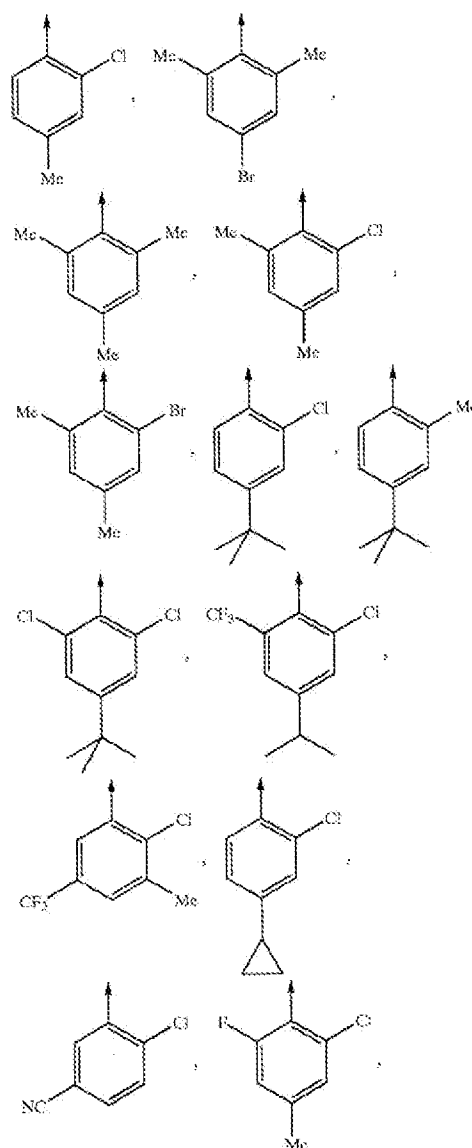
[0212] R^{14} , R^{15} ,

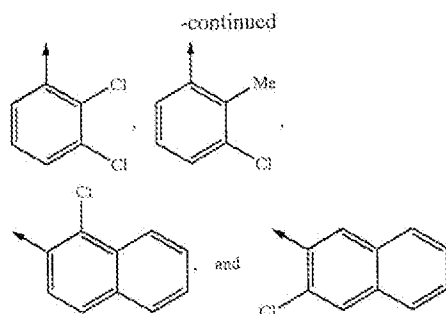
[0213] R^{31} , R^{32} ,

[0214] R^{33} are each independently selected from the group consisting of H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl- (C_{1-3}) alkyl, (C_{2-6}) alkenyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, halo, CF_3 , OCF_3 , OH, NO_2 , CN, SO_2NH_2 , $SO_2-(C_{1-4})$ alkyl, $C(O)OR^1$ wherein R^1 is H or (C_{1-4}) alkyl, or NR^2R^3 wherein R^2 and R^3 each independently is H or (C_{1-4}) alkyl; and

[0215] R^{30} represents H, Cl, Br, $COO(C_{1-4})$ alkyl.

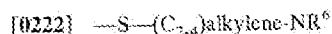
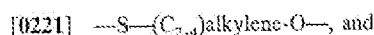
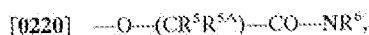
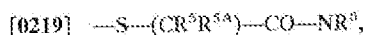
[0216] Most preferably R^{12} is selected from the group consisting of:





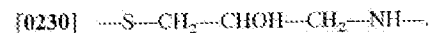
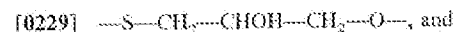
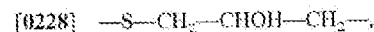
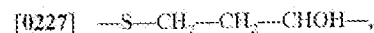
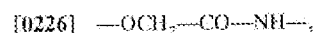
[0217] A method according to the present invention is preferred wherein the compound is a compound of formula 1 wherein X is O or S, most preferably S.

[0218] Furthermore, a method according to the present invention is preferred wherein the compound is a compound of formula 1 wherein —X—W— is a divalent radical selected from the group consisting of:



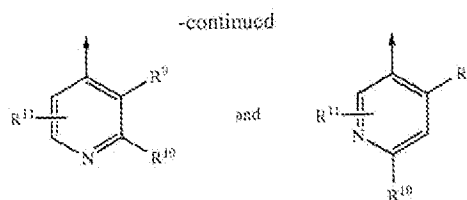
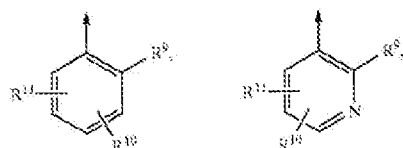
[0223] wherein R⁵ and R^{5A} each independently is H or (C₁₋₄)alkyl, R⁹ is H or (C₁₋₄)alkyl; and wherein the (C₂₋₄)alkylene group is optionally substituted with OH.

[0224] Most preferably —X—W— is a divalent radical selected from the group consisting of:



[0231] A most preferred meaning of the group W is CH(R¹⁵)C(O)NH wherein R¹⁵ is H or Me.

[0232] A method according to the present invention is preferred wherein the compound is a compound of formula 1 wherein Ar² is selected from the group consisting of



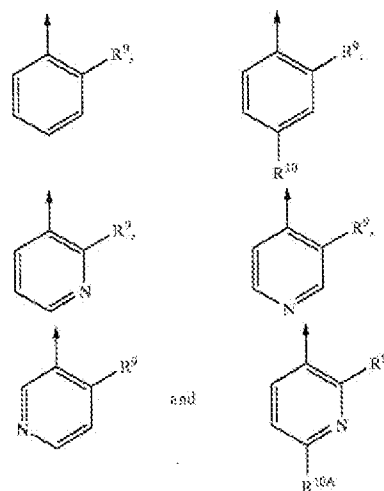
[0233] wherein R⁹ is (C₁₋₃)alkyl, halo or NO₂, and

[0234] R¹⁰, R¹¹ are independently of each other selected from the group consisting of H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₃)alkyl, (C₂₋₆)alkenyl, O(C₁₋₆)alkyl, S(C₁₋₆)alkyl, halo, CF₃, OCF₃, OH, NO₂, CN, —NR^{N1}R^{N2}, —C(O)R²¹, —(C₁₋₃)alkyl-C(O)R²¹, —C(O)OR²², —(C₁₋₃)alkyl-C(O)OR²², —SO₂—(C₁₋₃)alkyl-C(O)OR²², —(C₁₋₃)alkyl-C(O)NH₂, C(O)NH₂, —S(O)—(C₁₋₆)alkyl, —SO₂—(C₁₋₆)alkyl, —SO₂—phenyl, —SO₂—NH₂, phenyl, phenylmethyl, 2-, 3- or 4-pyridinyl, 1-pyrrolyl, whereby said phenyl, pyridinyl and pyrrolyl may have one or more substituents selected from the group consisting of halo, NO₂, C₁₋₃-alkyl and CF₃;

[0235] wherein R²¹ is (C₁₋₄)alkyl; R²² is H or (C₁₋₄)alkyl; and

[0236] wherein R^{N1}, R^{N2} each independently represent H or (C₁₋₆)alkyl, whereby R^{N1} and R^{N2} may be covalently bonded to each other to form together with the N-atom to which they are attached to a 4 to 7-membered heterocycle whereby the —CH₂—group at the position 4 of a 6 or 7-membered heterocycle may be replaced by —O—, —S— or —NR^{N3} wherein R^{N3} represents H, —C(O)OR²², (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₃₋₇)cycloalkyl-(C₁₋₃)alkyl, wherein R²² is H or (C₁₋₄)alkyl.

[0237] Most preferably Ar² is selected from the group consisting of



[0238] wherein R^9 is C_1 or NO_2 ;

[0239] wherein R^{10A} is C_{1-6} alkyl; and

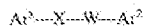
[0240] R^{10} is selected from the group consisting of (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl- (C_{1-6}) alkyl, (C_{2-6}) alkenyl, $O(C_{1-6})$ alkyl, $S(C_{1-6})$ alkyl, halo, CF_3 , OCF_3 , OH , NO_2 , CN , $-NR^{N1}R^{N2}$, $-C(O)R^{21}$, $-(C_{1-3})$ alkyl- $C(O)R^{21}$, $-C(O)OR^{22}$, $-(C_{1-3})$ alkyl- $C(O)OR^{22}$, $-SO_2-(C_{1-3})$ alkyl- $C(O)OR^{22}$, $-(C_{1-3})$ alkyl- $C(O)NH_2$, $C(O)NH_2$, $-S(O)-(C_{1-6})$ alkyl, $-SO_2-(C_{1-6})$ alkyl, $-SO_2$ -phenyl, $-SO_2-NH_2$, phenyl, phenylmethyl, phenyl- SO_2 -, 2-, 3- or 4-pyridinyl, 1-pyrrolyl, whereby said phenyl, pyridinyl and pyrrolyl may have one or more substituents selected from the group consisting of halo, NO_2 , C_{1-3} alkyl and CF_3 ;

[0241] wherein R^{21} is (C_{1-6}) alkyl; R^{22} is H or (C_{1-6}) alkyl;

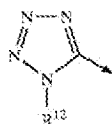
[0242] wherein R^{N1} , R^{N2} each independently represent H or (C_{1-6}) alkyl, whereby R^{N1} and R^{N2} may be covalently bonded to each other to form together with the N-atom to which they are attached to a 4 to 7-membered heterocycle whereby the $-CH_2-$ group at the position 4 of a 6 or 7-membered heterocycle may be replaced by $-O-$, $-S-$ or $-NR^{N3}$ wherein R^{N3} represents H, $-C(O)OR^{22}$, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{3-7}) cycloalkyl- (C_{1-3}) alkyl, wherein R^{22} is H or (C_{1-6}) alkyl.

[0243] In the following preferred embodiments of the second aspect of this invention which is related to new compounds are described.

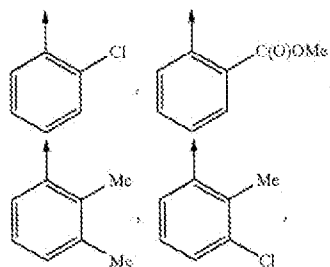
[0244] According to a first embodiment of the second aspect of the present invention, there are provided new compounds of the formula 1



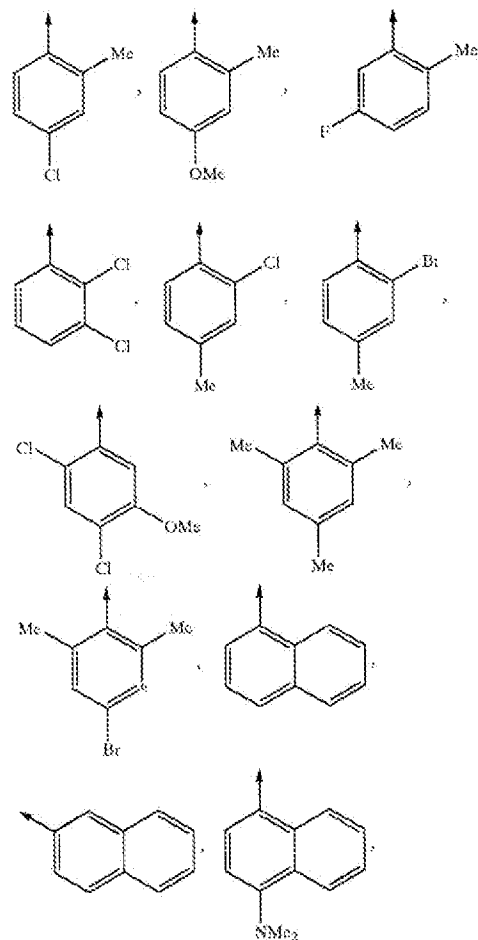
[0245] wherein Ar^1 is



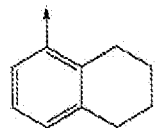
[0246] wherein R^{12} is selected from the group consisting of



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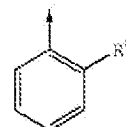
and



[0247] X is S;

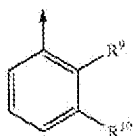
[0248] W is $CH_2C(O)NR^6$ wherein R^6 is H or (C_{1-6}) alkyl; and

[0249] Ar^2 is



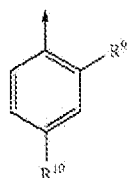
[0250] wherein R^9 is halo or NO_2 ; or

[0251] Ar^2 is



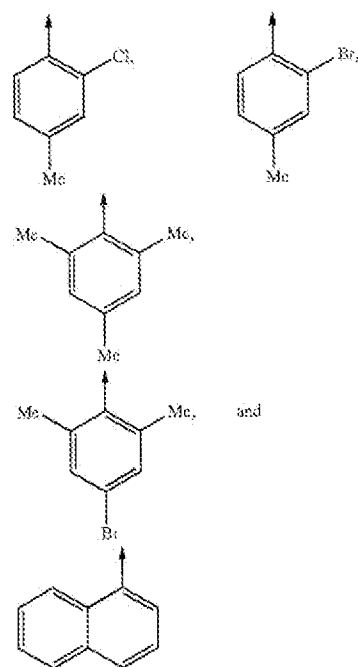
[0252] wherein R^9 is halo or NO_2 and R^{10} is halo; or

[0253] Ar^2 is



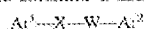
[0254] wherein R^9 is halo or NO_2 and R^{10} is OMe, halo, OH, NO_2 , phenyl, $\text{C}(\text{O})\text{OH}$ or $\text{C}(\text{O})\text{OMe}$.

[0255] Most preferably, new compounds are represented by the formula 1a wherein R^{12} is selected from the group consisting of

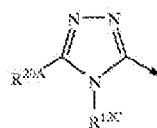


[0256] and X, W and Ar^2 are as defined in the last instance.

[0257] Alternatively, according to the first embodiment of the second aspect of the present invention new compounds of the formula 1 are provided

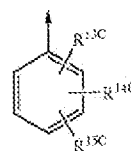


[0258] wherein Ar^1 is

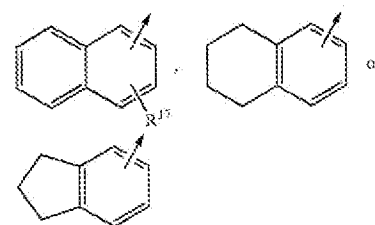


[0259] and

[0260] wherein R^{12C} is a phenyl of formula

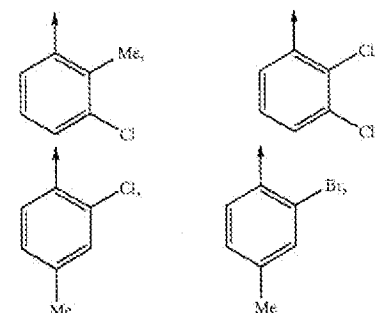


[0261] wherein R^{13C} , R^{14C} and R^{15C} each independently represents H, Me, Et, Pr, iPr, tBu, OMe, OEt, SMe, SEt, Br, Cl, F, CF_3 , NO_2 , $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{O})\text{OMe}$ or $\text{C}(\text{O})\text{OEt}$, provided that at least one of R^{13C} , R^{14C} and R^{15C} is other than hydrogen; or R^{12C} is

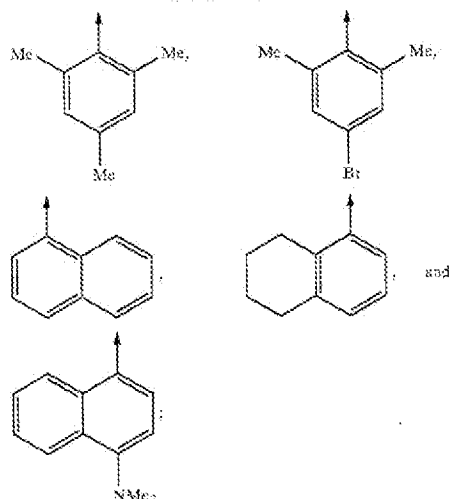


[0262] wherein R^{17} is selected from H, Me, OMe, Cl, F, CF_3 , NH_2 , NHMe or NMe_2 ; and R^{25A} is H, Me, Et, Pr or iPr.

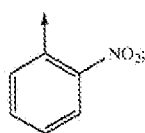
[0263] Most preferably R^{12} is selected from the group consisting of:



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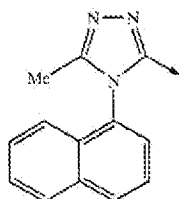


[0264] X is S; W is $\text{CH}_2\text{C(O)NH}$ and Ar^2 is



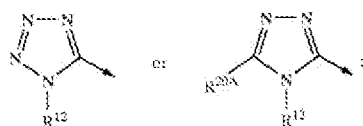
[0265] or

[0266] a compound of formula 1 wherein Ar^1 is



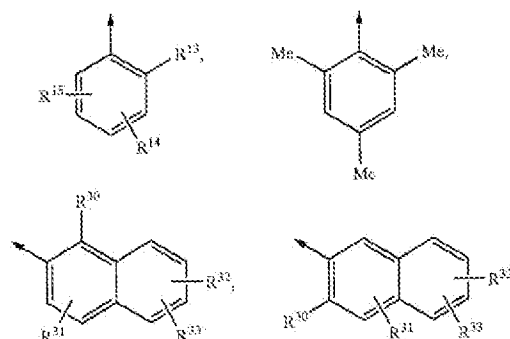
[0267] and X, W and Ar^2 are as defined in the last instance.

[0268] According to a second embodiment of the second aspect of the present invention, there are provided new compounds of the formula 1 wherein Ar^1 is



[0269] and

[0270] wherein R^{12} is selected from the group consisting of



[0271] wherein R^{13} , R^{14} , R^{15} , R^{20A} , R^{30} , R^{31} , R^{32} and R^{33} are as defined hereinbefore and hereinafter.

[0272] According to this second embodiment preferred meanings of the substituents are:

[0273] R^{13} represents Cl or Br; and

[0274] if R^6 is NO_2 , Cl or Br, then R^{13} may also represent F or CH_3 ;

[0275] R^{14} , R^{15} ,

[0276] R^{31} , R^{32} ,

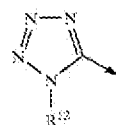
[0277] R^{33} are each independently selected from the group consisting of H, (C_{1-6}) alkyl, (C_{3-5}) cycloalkyl, (C_{3-7}) cycloalkyl- (C_{1-3}) alkyl, (C_{2-6}) alkenyl, $\text{O}-(\text{C}_{1-4})$ alkyl, $\text{S}-(\text{C}_{1-4})$ alkyl, halo, CF_3 , OCF_3 , OH, NO_2 , CN, SO_2NH_2 , $\text{SO}_2-(\text{C}_{3-4})$ alkyl, C(O)OR^1 wherein R^1 is H or (C_{1-4}) alkyl, or NR^2R^3 wherein R^2 and R^3 each independently is H or (C_{1-4}) alkyl; and

[0278] R^{30} represents Cl or Br.

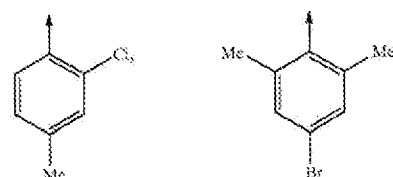
[0279] Most preferably W represents $\text{CH}_2\text{C(O)NH}$.

[0280] Most preferably $-\text{X}-$ is $-\text{S}-$.

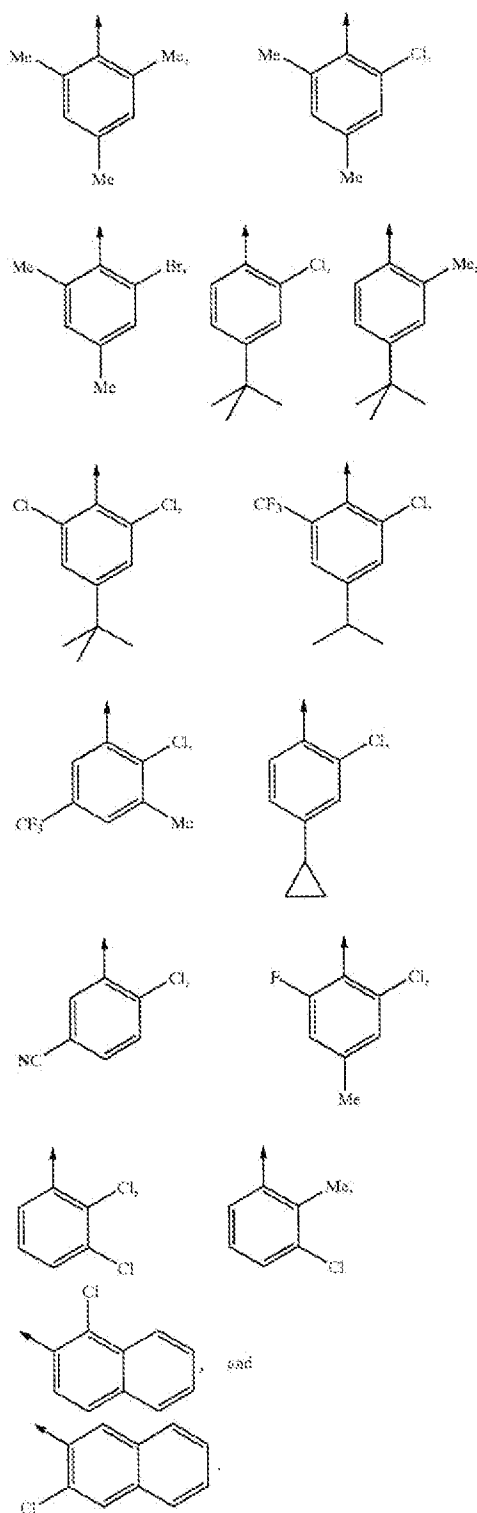
[0281] According to this second embodiment, most preferred are those compounds of the formula 1, wherein Ar^1 is:



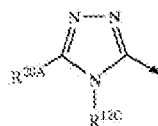
[0282] and wherein R^{12} selected from the group consisting of:



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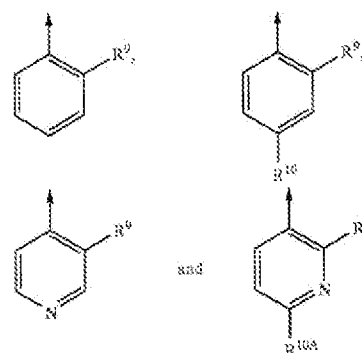


[0283] Furthermore, those compounds of formula 1 are preferred wherein Ar^1 is:



[0284] wherein R^{12C} has one of the most preferred meanings of R^{12} as defined above and R^{20A} is H, Me, Et, iPr or 2-hydroxy-ethyl, preferably R^{20A} is methyl or ethyl.

[0285] Furthermore those compounds of the second embodiment of the present invention are preferred wherein Ar^2 is selected from the group consisting of



[0286] wherein R^9 is C_1 or NO_2 and

[0287] R^{10A} is (C_{1-6}) alkyl;

[0288] R^{10} is selected from the group consisting of (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl- (C_{1-6}) alkyl, (C_{2-6}) alkenyl, $O(C_{1-6})$ alkyl, $S(C_{1-6})$ alkyl, halo, CF_3 , OCF_3 , OH , NO_2 , CN , $—NR^{N1}R^{N2}$, $—C(O)R^{21}$, $—(C_{1-3})$ alkyl- $C(O)R^{22}$, $—C(O)OR^{22}$, $—(C_{1-3})$ alkyl- $C(O)OR^{22}$, $—SO_2—(C_{1-3})$ alkyl- $C(O)OR^{22}$, $—(C_{1-3})$ alkyl- $C(O)NH_2$, $C(O)NH_2$, $—S(O)—(C_{1-6})$ alkyl, $—SO_2—(C_{1-6})$ alkyl, $—SO_2$ -phenyl, $—SO_2—NH_2$, phenyl, phenylmethyl, phenyl- SO_2 —, 2-, 3- or 4-pyridinyl, 1-pyrrolyl, whereby said phenyl, pyridinyl and pyrrolyl may have one or more substituents selected from the group consisting of halo, NO_2 , C_{1-3} -alkyl and CF_3 ;

[0289] wherein R^{21} is (C_{1-6}) alkyl; R^{22} is H or (C_{1-6}) alkyl;

[0290] wherein R^{N1} , R^{N2} each independently represent H or (C_{1-6}) alkyl, whereby R^{N1} and R^{N2} may be covalently bonded to each other to form together with the N-atom to which they are attached to a 4 to 7-membered heterocycle whereby the $—CH_2—$ group at the position 4 of a 6 or 7-membered heterocycle may be replaced by $—O—$, $—S—$ or $—NR^{N3}$, wherein R^{N3} represents H, $—C(O)OR^{22}$, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{3-7}) cycloalkyl- (C_{1-6}) alkyl, wherein R^{22} is H or (C_{1-6}) alkyl.

ceutical preparations may contain conventional adjuvants such as preservatives, stabilizers, emulsifiers, flavor-improvers, wetting agents, buffers, salts for varying the osmotic pressure and the like. Solid carrier material which can be used include, for example, starch, lactose, mannitol, methyl cellulose, microcrystalline cellulose, talc, silica, dibasic calcium phosphate, and high molecular weight polymers (such as polyethylene glycol).

[0301] For parenteral use, a compound of formula 1 can be administered in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable oil or a mixture of liquids, which may contain bacteriostatic agents, antioxidants, preservatives, buffers or other solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Additives of this type include, for example, tartrate, citrate and acetate buffers, ethanol, propylene glycol, polyethylene glycol, complex formers (such as EDTA), antioxidants (such as sodium bisulfite, sodium metabisulfite, and ascorbic acid), high molecular weight polymers (such as liquid polyethylene oxides) for viscosity regulation and polyethylene derivatives of sorbitol anhydrides. Preservatives may also be added if necessary, such as benzoic acid, methyl or propyl paraben, benzalkonium chloride and other quaternary ammonium compounds.

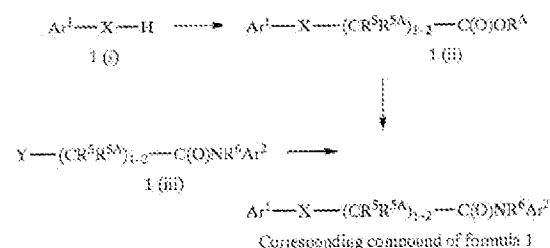
[0302] The compounds of this invention may also be administered as solutions for nasal application and may contain in addition to the compounds of this invention suitable buffers, tonicity adjusters, microbial preservatives, antioxidants and viscosity-increasing agents in an aqueous vehicle. Examples of agents used to increase viscosity are polyvinyl alcohol, cellulose derivatives, polyvinylpyrrolidone, polysorbates or glycerin. Microbial preservatives added may include benzalkonium chloride, thimerosal, chloro-butanol or phenylethyl alcohol.

[0303] Additionally, the compounds provided by the invention may be administrable by suppository.

[0304] Methodology and Synthesis

[0305] In general, the compounds of formula 1 are prepared by known methods from readily available starting materials, using reaction conditions known to be suitable for the reactants.

[0306] A process for preparing a compound of formula 1, wherein X is S or O and W is $(\text{CR}^{\text{SA}})_{1,2} \text{C(O)NR}^{\text{A}^2}$ as defined herein, is illustrated as follows:



[0307] wherein Ar^1 and Ar^2 are as defined herein, X is S or O, R^{A} is H or (C_{1-4}) alkyl and Y is halo, e.g. Br or Cl.

[0308] The process comprises:

[0309] a) reacting a thiol or alcohol of formula $\text{Ar}^1\text{---X---H}$ {1 (i)} with an *o*-halo alkanolic alkyl ester of formula $\text{Y---}(\text{CR}^{\text{SA}})_{1,2}\text{---C(O)OR}^{\text{A}}$ wherein Y is halo and R^{A} is (C_{1-4}) alkyl, in the presence of a base, to obtain the corresponding ester of formula $\text{Ar}^1\text{---X---}(\text{CR}^{\text{SA}})_{1,2}\text{---C(O)OR}^{\text{A}}$ {1 (ii)}, followed by hydrolysis of the ester to the corresponding acid wherein $\text{R}^{\text{A}}=\text{H}$, and coupling the latter acid with an aromatic amine of general formula $\text{HNR}^{\text{A}^2}\text{---Ar}^2$ in the presence of a coupling agent to obtain the corresponding compound of formula 1 wherein Ar^1 and Ar^2 are as defined herein, X is S or O and W is $(\text{CR}^{\text{SA}})_{1,2}\text{---C(O)---NR}^{\text{A}^2}$ as defined herein; or

[0310] b) reacting a thiol or alcohol of formula $\text{Ar}^1\text{---X---H}$ wherein Ar^1 is as defined herein and X is S or O with an anilide of formula $\text{Y---}(\text{CR}^{\text{SA}})_{1,2}\text{---C(O)NR}^{\text{A}^2}$ in the presence of a base to obtain the corresponding compound of formula 1.

[0311] The requisite starting material of formula $\text{Ar}^1\text{---X---H}$ can be prepared readily by reacting a commercially available aromatic isocyanate or isothiocyanates with sodium azide to give directly the desired starting material. The aromatic amine $\text{HNR}^{\text{A}^2}\text{---Ar}^2$ is either available commercially or can be prepared by known methods.

[0312] The requisite aromatic amide of formula $\text{Y---}(\text{CR}^{\text{SA}})_{1,2}\text{---C(O)NR}^{\text{A}^2}\text{---Ar}^2$ can be prepared readily by known methods from commercially available amines; for example, see example 2 hereinafter.

[0313] Although several well known coupling agents can be used in the preceding process, phosphorus oxychloride has been found to be practical and efficient.

[0314] Processes and reactants for preparing other compounds of formula 1 are illustrated further by the examples hereinafter.

EXAMPLES

[0315] The present invention is illustrated in further detail by the following non-limiting examples. All reactions were performed in a nitrogen or argon atmosphere unless otherwise stated. Room temperature is 18 to 22° C. (degrees Celsius). Solution percentages or ratios express a volume to volume relationship, unless stated otherwise.

[0316] Abbreviations or symbols used herein include:

[0317] Boc: tert-butoxycarbonyl;

[0318] CHAPS: 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate;

[0319] DEAD: diethyl azodicarboxylate;

[0320] DIAD: diisopropyl azodicarboxylate;

[0321] DMF: N,N-dimethylformamide;

[0322] DMSO: dimethylsulfoxide;

[0323] dppf: 1,1'-bis(diphenylphosphino)ferrocene;

[0324] DPPBE: 4-diphenylphosphanylbenzoic acid, 2-(trimethylsilyl)ethyl ester;

[0325] DTT: DL-dithiothreitol;

- [0326] Et₂O: diethyl ether;
 [0327] EtOAc: ethyl acetate;
 [0328] GSH: glutathione;
 [0329] HPLC: high performance liquid chromatography;
 [0330] iPr: isopropyl;
 [0331] LDA: Lithium diisopropylamide;
 [0332] MCPBA: meta-chloroperoxybenzoic acid;
 [0333] Me: methyl;
 [0334] MeOH: methanol;
 [0335] MeCN: acetonitrile;
 [0336] Ph: phenyl;
 [0337] TBAF: tetrabutylammonium fluoride;
 [0338] TFA: trifluoroacetic acid;
 [0339] THF: tetrahydrofuran;

[0340] Syntheses

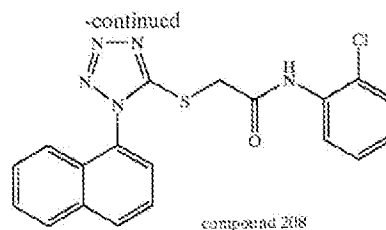
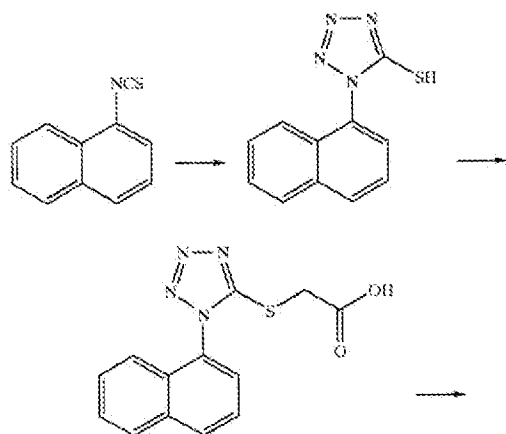
[0341] The following examples illustrate methods for preparing compounds of the invention.

Example 1

Entry 208

N-(2-Chlorophenyl)-2-{{1-(1-naphthalenyl)-1H-tetrazol-5-yl}thio}acetamide

[0342]



a) 1,2-Dihydro-1-(1-naphthalenyl)-5H-tetrazole-5-thione

[0343] To a solution of NaN₃ (1.76 g, 27.0 mmol) in a mixture of 1,4-dioxane (25 mL) and water (25 mL) was added 1-naphthalenylisothiocyanate (5.00 g, 27.0 mmol) at room temperature. The yellow solution containing a white solid was heated at 102° C. for 2 h. The reaction mixture was then cooled to room temperature and aqueous 1 N HCl solution was added until pH 2 was reached. The aqueous mixture was extracted with EtOAc (250 mL). The organic layer was extracted with aqueous 1 N NaOH solution. The aqueous layer was acidified with aqueous 6 N HCl solution and a white precipitate formed. The suspension was filtered and the resulting solid was triturated with Et₂O/hexane (1/1) to give the title compound (3.89 g, 63% yield) as an off white solid.

b) 2-{{1-(1-Naphthalenyl)-1H-tetrazol-5-yl}thio}acetic acid

[0344] Pyridine (0.83 mL, 10.3 mmol) and 1,2-dihydro-1-(1-naphthalenyl)-5H-tetrazole-5-thione (2.14 g, 9.38 mmol) were added to a solution of methyl 2-bromoacetate (977 μ L, 10.3 mmol) in DMSO (50 mL). The resulting light yellow solution was stirred at room temperature for 2 h. The reaction mixture was then diluted with EtOAc (300 mL) and was successively washed with water (2x250 mL) and brine (100 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The crude ester was dissolved in THF and aqueous 1 N NaOH solution was added. The solution was stirred at room temperature for 30 min. The THF was evaporated under reduced pressure and the residue was dissolved in aqueous 1 N NaOH solution. The solution was slowly acidified to pH 2 at 0° C. with aqueous 1 N HCl solution. The suspension was filtered and the resulting solid was rinsed with water and dried under reduced pressure to give the title compound (2.48 g, 92% yield) as a white solid.

c) N-(2-Chlorophenyl)-2-{{1-(1-naphthalenyl)-1H-tetrazol-5-yl}thio}acetamide

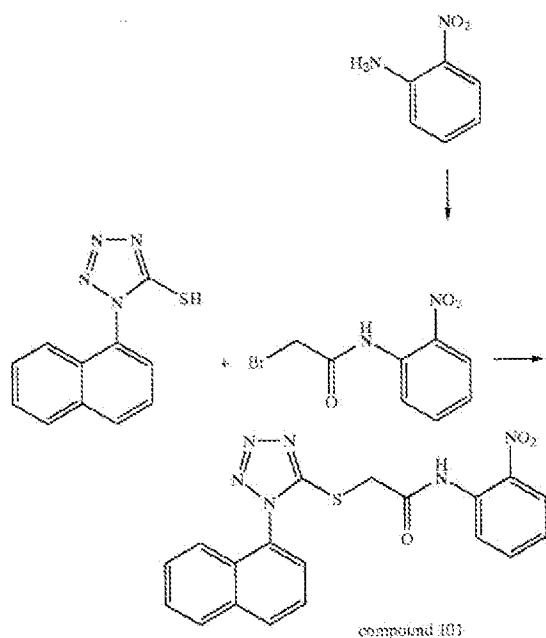
[0345] 2-{{1-(1-Naphthalenyl)-1H-tetrazol-5-yl}thio}acetic acid (500 mg, 1.75 mmol) and 2-chloroaniline (202 μ L, 1.92 mmol) were dissolved in dry pyridine (8 mL). This solution was cooled to 0° C. and POCl₃ (0.179 mL) was added dropwise. The mixture was stirred at 0° C. for 1 h, quenched with a few drops of water, and concentrated under reduced pressure. The crude product was dissolved in CH₂Cl₂ (100 mL) and the resulting solution was successively washed with water (2x30 mL) and brine (30 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (CH₂Cl₂:(CH₃)₂CO, 95:5) to afford the title compound (643 mg, 85% yield) as a solid.

Example 2

Entry 101

2-{{1-(1-Naphthalenyl)-1H-tetrazol-5-yl}thio}-N-(2-nitrophenyl)acetamide

[0346]



a) 2-Bromo-N-(2-nitrophenyl)acetamide

[0347] 2-Bromoacetyl bromide (173 μ L, 1.99 mmol) was added dropwise to a solution of 2-nitroaniline (250 mg, 1.81 mmol) and pyridine (293 μ L) in CH_2Cl_2 (9 mL). The reaction mixture was stirred at room temperature for 45 min. The mixture was then diluted with CH_2Cl_2 (10 mL), washed with aqueous 1 N HCl solution (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield the title compound (431 mg, 92% yield) as an orange solid.

b) 2-{{1-(1-Naphthalenyl)-1H-tetrazol-5-yl}thio}-N-(2-nitrophenyl)acetamide

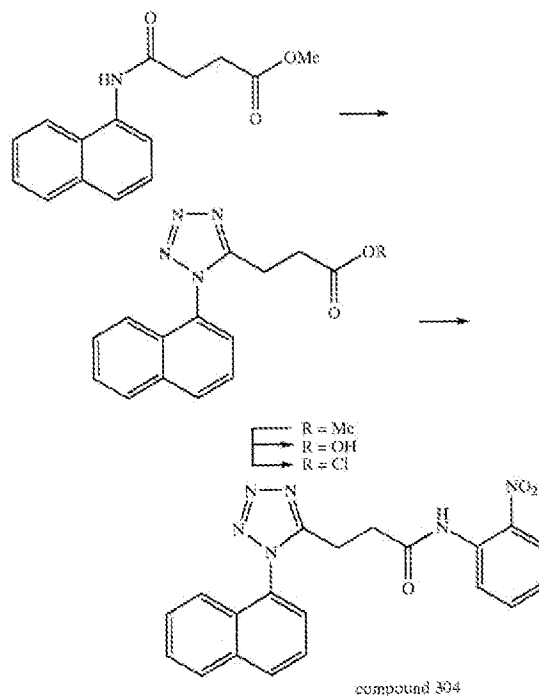
[0348] To a solution of 2-bromo-N-(2-nitrophenyl)acetamide (186 mg, 0.718 mmol) in DMSO (4 mL) was added pyridine (116 μ L, 1.43 mmol) followed by 1,2-dihydro-1-(1-naphthalenyl)-5H-tetrazole-5-thione (164 mg, 0.718 mmol). The dark brown solution was stirred at room temperature for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (40 mL) and washed with water (2x40 mL), brine, dried (Na_2SO_4), filtered and directly loaded onto silica gel. The crude sample was purified by flash chromatography (EtOAc) to afford 140 mg of a light yellow solid which was lyophilized from water-MeCN to afford (136 mg, 47% yield) of the title compound.

Example 3

Entry 304

1-(1-Naphthalenyl)-N-(2-nitrophenyl)-1H-tetrazole-5-propanamide

[0349]



a) 1-(1-Naphthalenyl)-1H-tetrazole-5-propanoic acid

[0350] A 0.5 M DPPBE solution in THF (20.0 mL, 10.0 mmol), DIAD (1.97 mL, 10.0 mmol) and TMSN_3 (1.33 mL, 10.0 mmol) were successively added to a solution of methyl 4-{{1-(1-naphthalenyl)amino}4-oxobutanoate (1.29 g, 5.00 mmol) in THF (30 mL). The reaction mixture was stirred at room temperature for 3 days. A 1.0 M TBAF solution in THF (5.00 mL, 5.00 mmol; additional 5.00 mL added after 5.5 h) was added and the mixture was stirred at room temperature for 6.5 h. The mixture was concentrated under reduced pressure and the residue was taken in EtOAc (250 mL). The solution was successively washed with aqueous 1 N HCl solution (25 mL), water (25 mL), aqueous 1 N NaOH solution (2x15 mL), water (15 mL) and brine (15 mL), dried (MgSO_4), filtered and concentrated under reduced pressure. The residue was partially purified by flash chromatography (hexane:EtOAc: CH_2Cl_2 , 3:1:1) to yield the impure ester. The ester was dissolved in THF (10 mL) and MeOH (5 mL) and aqueous 1 N NaOH solution (3.0 mL, 3.00 mmol) was added to the solution. The mixture was heated at 60° C. for 1 h. The organic solvents were removed under reduced pressure. The resulting aqueous solution was washed with EtOAc (2x25 mL). The aqueous layer was rendered acidic by addition of aqueous 1 N HCl solution (15 mL) and was

extracted with EtOAc (50 mL). The organic layer was washed with water and brine, dried (MgSO_4), filtered and concentrated under reduced pressure to give the title compound (768 mg, 58% yield) as a white solid.

b) 1-(1-Naphthalenyl)-1H-tetrazole-5-propanoyl chloride

[0351] A solution of $(\text{COCl})_2$ (310 μL , 3.45 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a suspension of 1-(1-naphthalenyl)-1H-tetrazole-5-propanoic acid (738 mg, 2.75 mmol) in CH_2Cl_2 (50 mL) and DMF (50 μL). The reaction mixture was stirred at room temperature for 1.5 h. The mixture was concentrated to give the title compound (789 mg, 100% yield).

c) 1-(1-Naphthalenyl)-N-(2-nitrophenyl)-1H-tetrazole-5-propanamide

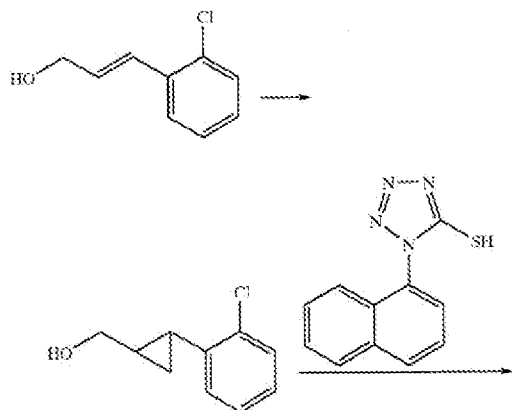
[0352] A solution of 1-(1-naphthalenyl)-1H-tetrazole-5-propanoyl chloride (112 mg, 0.39 mmol) in THF (2 mL) was added slowly to a solution of 2-nitroaniline (54.5 mg, 0.39 mmol) and pyridine (79.3 μL , 0.98 mmol) in THF (2 mL) at room temperature. The mixture was stirred at room temperature for 16 h. The mixture was diluted with EtOAc (50 mL). The solution was successively washed with aqueous 1 N HCl solution (10 mL), water (10 mL), aqueous saturated NaHCO_3 solution (2x5 mL) and brine (10 mL), dried (MgSO_4), filtered and concentrated under reduced pressure. The residue was triturated with Et_2O :hexane (1:1) to give, after drying, the title compound (72 mg, 47% yield) as a yellow solid.

Example 4

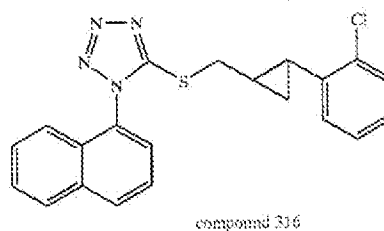
Entry 316

trans-5-{{[2-(2-Chlorophenyl)cyclopropyl]methyl}thio}-1-(1-naphthalenyl)-1H-tetrazole

[0353]



-continued



a) trans-3-(2-Chlorophenyl)-2-propen-1-ol

[0354] A solution of 2-chlorocinnamic acid (5.00 g, 27.4 mmol) in THF (50 mL) was slowly added to a suspension of NaBH_4 (1.24 g, 32.9 mmol) in THF (50 mL) at room temperature. The mixture was stirred until evolution of gas ceased. A solution of 12 (3.47 g, 13.7 mmol) in THF (50 mL) was then added and the mixture was stirred at room temperature for 1 h. Aqueous 3 N HCl solution (10 mL) was added carefully and the mixture was extracted with Et_2O . The combined organic layers were successively washed with aqueous 1 N NaOH solution and brine, dried (MgSO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2 : $(\text{CH}_3)_2\text{CO}$, 95:5) to yield the title compound (2.86 g, 62% yield).

b) trans-2-(2-Chlorophenyl)cyclopropanemethanol

[0355] $\text{Pd}(\text{OAc})_2$ (13.3 mg, 0.06 mmol) was added to a solution of trans-3-(2-chlorophenyl)-2-propen-1-ol (100 mg, 0.59 mmol) in a solution of CH_2N_2 in Et_2O (ca. 0.6 M, 25 mL). The reaction mixture was stirred at room temperature for 1 h. An additional amount of CH_2N_2 solution in Et_2O (25 mL) was added and the mixture was stirred for 1 h. The mixture was filtered through diatomaceous earth and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2 : $(\text{CH}_3)_2\text{CO}$, 95:5) to yield the title compound (85.5 mg, 79% yield).

c) trans-5-{{[2-(2-Chlorophenyl)cyclopropyl]methyl}thio}-1-(1-naphthalenyl)-1H-tetrazole

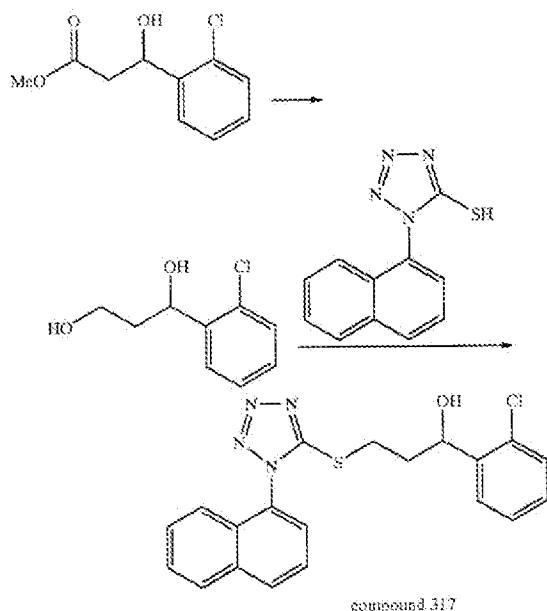
[0356] DIAD (87 μL , 0.44 mmol) was added dropwise to a solution of 1,2-dihydro-1-(1-naphthalenyl)-5H-tetrazole-5-thione (84.0 mg, 0.37 mmol), trans-2-(2-chlorophenyl)cyclopropanemethanol (80.5 mg, 0.44 mmol), and PPh_3 (116 mg, 0.44 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h then was concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2 : $(\text{CH}_3)_2\text{CO}$, 95:5) to give the title compound (81 mg, 56% yield) as a white solid.

Example 5

Entry 317

5-{{3-(2-Chlorophenyl)-3-hydroxypropyl}thio}-1-(1-naphthalenyl)-1H-tetrazole

[0357]



a) Methyl 2-chloro-β-hydroxybenzenepropanoate

[0358] Methyl acetate (5.09 mL, 64.0 mmol) was added dropwise to a cold (-78°C) solution of LDA [prepared at 0°C from $i\text{-Pr}_2\text{NH}$ (10.5 mL, 74.7 mmol) and 2.0 M $n\text{-BuLi}$ in hexane (37.3 mL, 74.7 mmol)] in THF (50 mL). After 45 min, the enolate solution was added via cannula to a cold (-78°C) solution of 2-chlorobenzaldehyde (3.00 g, 21.3 mmol) in THF (50 mL). The reaction mixture was stirred at -78°C for 1 h. Aqueous saturated NH_4Cl solution (15 mL) was then added and the mixture was allowed to warm slowly to room temperature. The mixture was concentrated under reduced pressure. The residue was taken in Et_2O (300 mL) and the resulting solution was washed with water (2x50 mL) and brine (50 mL), dried (MgSO_4), filtered and concentrated under reduced pressure. The residue was partially purified by flash chromatography ($\text{CH}_2\text{Cl}_2:(\text{CH}_3)_2\text{CO}$, 95:5) to give the title compound (2.9 g, 63% yield).

b) 1-(2-Chlorophenyl)-1,3-propanediol

[0359] LiAlH_4 (1.28 g, 33.8 mmol) was added to an ice-cold solution of methyl 2-chloro-β-hydroxybenzenepropanoate (2.90 g, 13.5 mmol) in THF (70 mL). The reaction mixture was stirred at 0°C for 2 h. Water (4.0 mL), aqueous 10% NaOH solution (4.0 mL) and water (12 mL) were successively added to the mixture. Et_2O (300 mL) was added and the mixture was washed with water (2x100 mL) and brine (100 mL), dried (MgSO_4), filtered and concen-

trated under reduced pressure. The residue was purified by flash chromatography (hexane: EtOAc , 1:1) to give the title compound (829 mg, 33% yield).

c) 5-{{3-(2-Chlorophenyl)-3-hydroxypropyl}thio}-1-(1-naphthalenyl)-1H-tetrazole

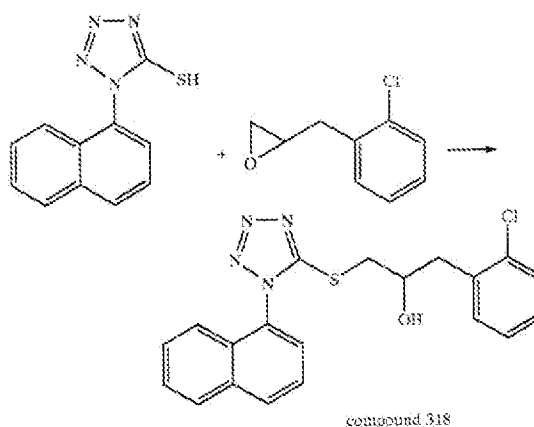
[0360] DIAD (82 μL , 0.42 mmol) was added dropwise to a solution of 1,2-dihydro-1-(1-naphthalenyl)-5H-tetrazole-5-thione (80.0 mg, 0.35 mmol), 1-(2-chlorophenyl)-1,3-propanediol (65.4 mg, 0.35 mmol), and PPh_3 (110 mg, 0.42 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h then was concentrated under reduced pressure. The residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2:(\text{CH}_3)_2\text{CO}$, 95:5) to give the title compound (70 mg, 50% yield) as a white solid.

Example 6

Entry 318

5-{{3-(2-Chlorophenyl)-2-hydroxypropyl}thio}-1-(1-naphthalenyl)-1H-tetrazole

[0361]



a) 2-Chloro-1-(2,3-epoxypropyl)benzene

[0362] MCPBA (826 mg, 3.83 mmol) was added portionwise to an ice-cold solution of 2-chloro-1-allylbenzene (487 mg, 3.19 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 16 h. Aqueous 10% Na_2CO_3 solution (10 mL) and CH_2Cl_2 (100 mL) were added. The solution was successively washed with aqueous 10% $\text{Na}_2\text{S}_2\text{O}_3$ (2x40 mL) and brine (40 mL), dried (MgSO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane: EtOAc , 8:2) to give the title compound (512 mg, 95% yield).

b) 5-{{3-(2-Chlorophenyl)-2-hydroxypropyl}thio}-1-(1-naphthalenyl)-1H-tetrazole

[0363] A solution of 1,2-dihydro-1-(1-naphthalenyl)-5H-tetrazole-5-thione (50.0 mg, 0.22 mmol), 2-chloro-1-(2,3-epoxypropyl)benzene (36.9 mg, 0.22 mmol) and Et_3N (0.15 mL, 1.10 mmol) in MeOH (5 mL) was heated at reflux for

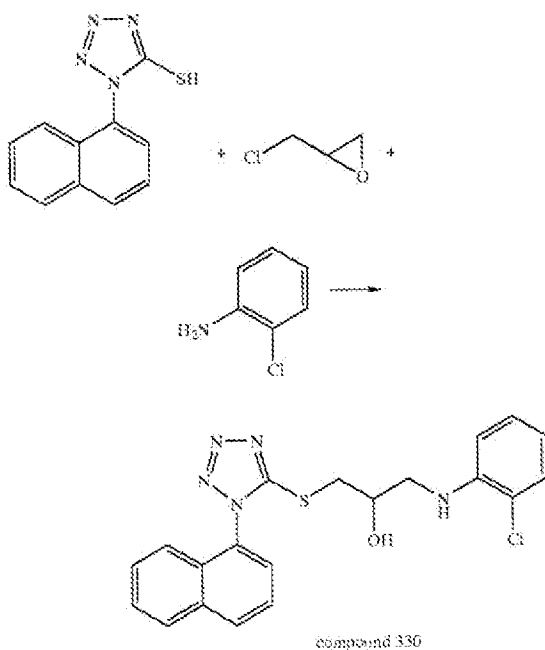
2 h. The mixture was concentrated under reduced pressure and the residue was purified by HPLC using a gradient of MeCN/H₂O containing TFA (0.1%) (CombiPrep ODS-AQ 50x20 mm, 5 μ , 120 Å). The pure fractions were concentrated to give the title compound (12 mg, 14% yield) as a colorless solid.

Example 7

Entry 330

5-{{3-[(2-chlorophenyl)amino]-2-hydroxypropyl}thio}-1-(1-naphthalenyl)-1H-tetrazole

[0364]



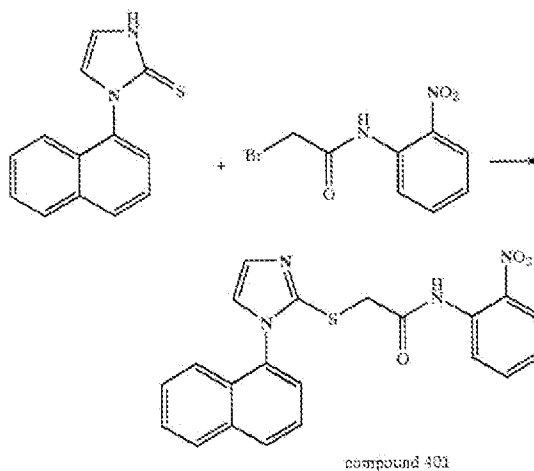
[0365] A solution of 2-chloroaniline (46.1 μ L, 0.44 mmol), epichlorohydrin (51.4 μ L, 0.66 mmol) and Et₃N (0.30 mL, 2.19 mmol) in MeOH (10 mL) was heated at reflux for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography. A solution of the intermediate obtained (93.4 mg), 1,2-dihydro-1-(1-naphthalenyl)-5H-tetrazole-5-thione (50.0 mg, 0.22 mmol) and Et₃N (0.30 mL, 2.19 mmol) in MeOH (10 mL) was heated at reflux for 3 days. The mixture was concentrated under reduced pressure and the residue was purified by HPLC using a gradient of MeCN/H₂O containing TFA (0.1%) (CombiPrep ODS-AQ 50x20 mm, 5 μ , 120 Å). The pure fractions were concentrated to give the title compound (11.7 mg, 13% yield) as a pale yellow solid.

Example 8

Entry 401

2-{{4-[(1-naphthalenyl)-1H-imidazol-2-yl]thio}-N-(2-nitrophenyl)acetamide

[0366]



a) 1,3-Dihydro-1-(1-naphthalenyl)-2H-imidazole-2-thione

[0367] A solution of 1-naphthalenylthioisocyanate (893 mg, 4.82 mmol) and 2-aminoacetaldehyde diethyl acetal (0.70 mL, 4.85 mmol) in toluene (10 mL) was stirred at room temperature for 1 h. Aqueous 12 N HCl solution (0.2 mL) was added and the mixture was heated at 110° C. for 3 h and then stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure. The residue was triturated with hot EtOAc to give the title compound (608 mg, 56% yield).

b) 2-{{4-[(1-Naphthalenyl)-1H-imidazol-2-yl]thio}-N-(2-nitrophenyl)acetamide

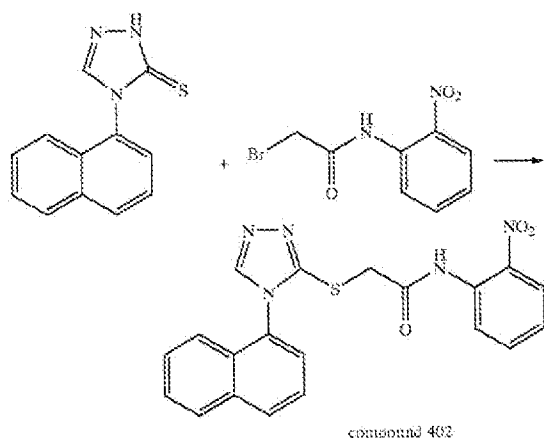
[0368] A solution of 1,3-dihydro-1-(1-naphthalenyl)-2H-imidazole-2-thione (129 mg, 0.50 mmol) in DMSO (2 mL) was added slowly to a solution of 2-bromo-N-(2-nitrophenyl)acetamide (113 mg, 0.50 mmol) and pyridine (121 μ L, 1.49 mmol) in DMSO (1 mL) at room temperature. The mixture was stirred at room temperature for 18 h, then diluted with water and extracted with EtOAc (50 mL). The organic layer was washed with water (3x) and brine, dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by HPLC using a gradient of MeCN/H₂O containing TFA (0.06%) (CombiPrep ODS-AQ 50x20 mm, 5 μ , 120 Å). The pure fractions were combined and lyophilized to give the title compound (8.4 mg, 4% yield).

Example 9

Entry 402

2-{{4-(1-Naphthalenyl)-4H-1,2,4-triazol-3-yl}thio}-
N-(2-nitrophenyl)acetamide

[0369]



a) 2,4-Dihydro-4-(1-naphthalenyl)-3H-1,2,4-triazole-3-thione

[0370] A solution of 4-(1-naphthalenyl)-3-thiosemicarbazide (4.01 g, 18.4 mmol) and N,N-dimethylformamide dimethyl acetal (2.50 mL, 18.8 mmol) in 1,4-dioxane (40 mL) was stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure. The residue was taken in hexane and Et₂O and the solution was stirred until a suspension was obtained. The suspension was filtered and the solid was triturated with hexane:Et₂O (4:1), then was dried under reduced pressure to give the title compound (4.19 g, 90% yield) as a beige solid.

b) 2-{{4-(1-Naphthalenyl)-4H-1,2,4-triazol-3-yl}thio}-N-(2-nitrophenyl)acetamide

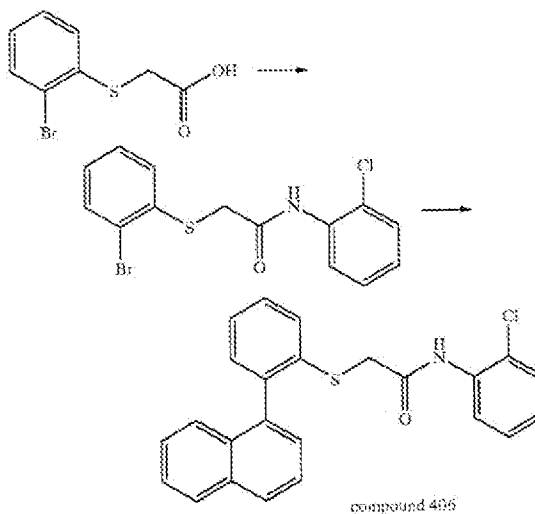
[0371] A solution of 2,4-dihydro-4-(1-naphthalenyl)-3H-1,2,4-triazole-3-thione (129 mg, 0.50 mmol) in DMSO (2 mL) was added slowly to a solution of 2-bromo-N-(2-nitrophenyl)acetamide (113 mg, 0.50 mmol) and pyridine (121 μ L, 1.49 mmol) in DMSO (1 mL) at room temperature. The mixture was stirred at room temperature for 18 h, then diluted with water and extracted with EtOAc (50 mL). The organic layer was washed with water (3 \times) and brine, dried (MgSO₄), filtered and concentrated under reduced pressure. A mixture of Et₂O and hexane (1:1) was added, the resulting suspension was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by HPLC using a gradient of MeCN/H₂O containing TFA (0.06%) (CombiPrep ODS-AQ 50 \times 20 mm, 5 μ , 120 \AA). The pure fractions were combined and concentrated to give the title compound (4.5 mg, 2% yield).

Example 10

Entry 406

2-{{2-(1-Naphthalenyl)phenyl}thio}-N-(2-chlorophenyl)acetamid

[0372]



a) 2-{{2-(2-Bromophenyl)thio}acetic acid

[0373] 2-Bromothiophenol (4.00 g, 21.6 mmol) was added to a solution of methyl 2-bromoacetate (2.20 mL, 23.3 mmol) and pyridine (1.88 mL, 23.3 mmol) in DMSO (50 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc (300 mL) and the resulting solution was washed with water (2 \times 250 mL) and brine (100 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was dissolved in THF (50 mL), aqueous 1 N NaOH solution (25 mL, 25 mmol) was added and the mixture was stirred at room temperature for 45 min. The mixture was concentrated and the aqueous solution was diluted with aqueous 1 N NaOH solution. The solution was cooled to 0 $^{\circ}$ C. and was slowly rendered acidic (pH=2) by addition of aqueous 1 N HCl solution. The resulting suspension was filtered, the solid was washed with water and dried under reduced pressure to give the title compound (3.71 g, 71% yield) as a white solid.

b)

2-{{2-(2-Bromophenyl)thio}-N-(2-chlorophenyl)acetamide

[0374] PCl₅ (0.39 mL, 4.45 mmol) was added to an ice-cold solution of 2-{{2-(2-bromophenyl)thio}acetic acid (1.00 g, 4.05 mmol) and 2-chloroaniline (0.47 mL, 4.45 mmol) in pyridine (15 mL). The reaction mixture was stirred at room temperature for 30 min. Water (few drops) was added and the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (CH₂Cl₂) to give the title compound (957 mg, 66% yield) as a yellow solid.

c) 2-{{2-(1-Naphthaleenyl)phenyl}thio}-N-(2-chlorophenyl)acetamide

[0375] $\text{PdCl}_2(\text{dppf})$ (1:1 complex with CH_2Cl_2 , 41.0 mg, 56.0 μmol) and dppf (31.1 mg, 56.1 μmol) were added to a degassed (N_2 , 45 min) solution of 2-{{2-bromophenyl}thio}-N-(2-chlorophenyl)acetamide (200 mg, 0.56 mmol), 1-naphthaleneboronic acid (116 mg, 0.67 mmol) and K_3PO_4 (357 mg, 1.68 mmol) in 1,4-dioxane (5 mL). The reaction mixture was heated at 100° C. for 3 h. The cooled mixture was diluted with EtOAc (50 mL) and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2:(\text{CH}_3)_2\text{CO}$, 98:2) to give the title compound (147 mg, 65% yield) as a pale orange solid.

[0376] Tables 1 to 8 illustrate further compounds of the present invention, which can be synthesized in analogy to the methods as described hereinbefore, optionally modified by procedures known to the one skilled in the art.

TABLE 1

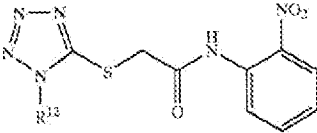
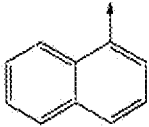
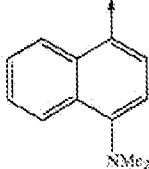
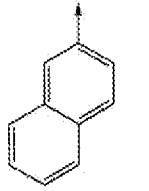
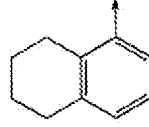
		
Entry #	R ¹²	MS ES ⁺ (MH)
101		407
102		450
103		407
104		411

TABLE 1-continued

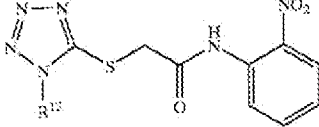
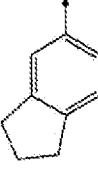
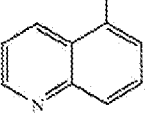
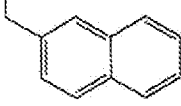
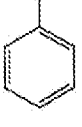
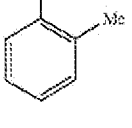
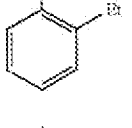
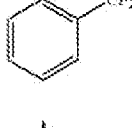
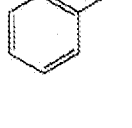
		
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106		408
107		421
108		357
109		371
110		385
111		425
112		399

TABLE 1-continued

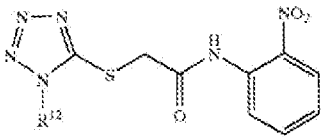
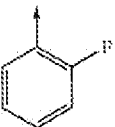
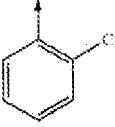
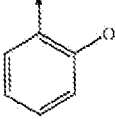
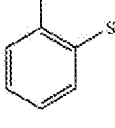
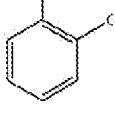
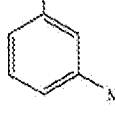
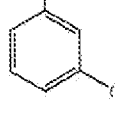
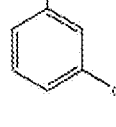
		
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115		387
116		403
117		415
118		371
119		391/393
120		415

TABLE 1-continued

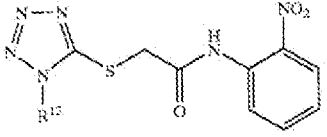
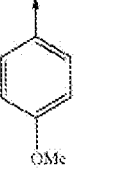
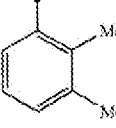
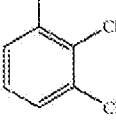
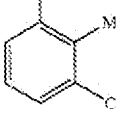
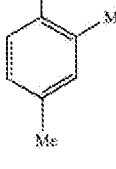
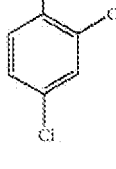
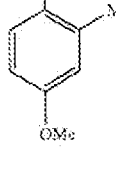
		
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124		405/407
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126		425/427/429
127		401

TABLE 1-continued

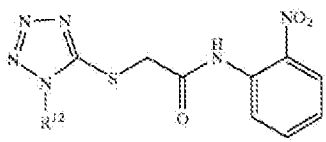
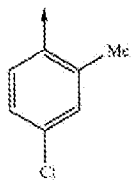
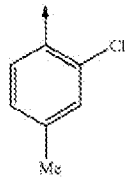
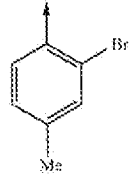
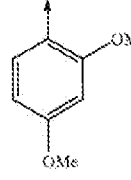
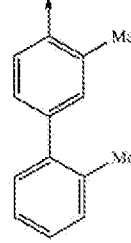
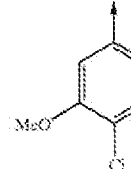
		
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133		455/457/459

TABLE 1-continued

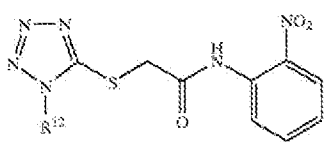
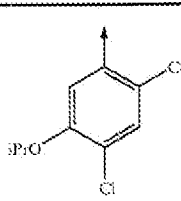
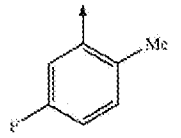
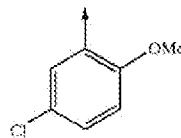
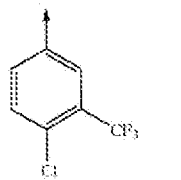
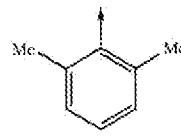
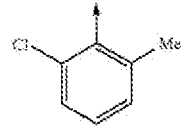
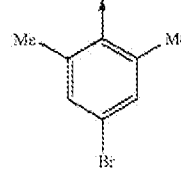
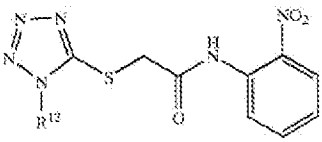
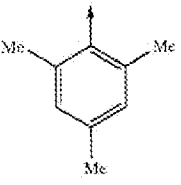

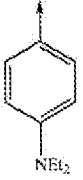
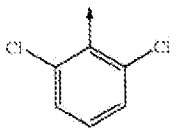
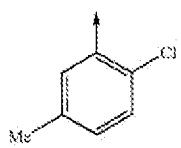
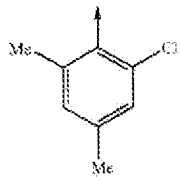
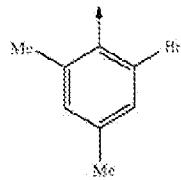
		
Entry #	R ¹²	MS ES ⁺ (MH)
134		483/485/487
135		387 MS ES ⁺ (M - H)
136		421/423
137		457/459 MS ES ⁺ (M - H)
138		385
139		405/407
140		461/463 MS ES ⁺ (M - H)

TABLE 1-continued

		
Entry #	R ¹²	MS ES ⁺ (MH ⁺)
141		399
142		399
143		428
144		425/427/429
145		405/407
146		419/421
147		463/465

[0377]

TABLE 2

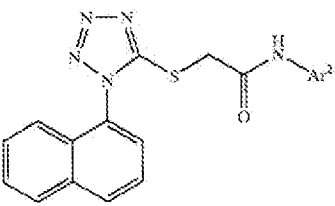
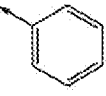
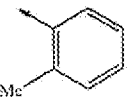
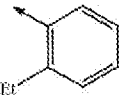
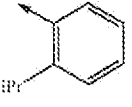
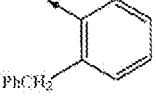
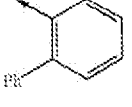
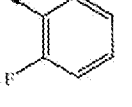
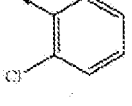
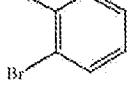
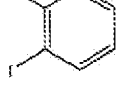
		
Entry #	Ar ³	MS ES ⁺ (MH ⁺)
201		362
202		376
203		390
204		404
205		452
206		438
207		380
208		396/398
209		440/442
210		488

TABLE 2-continued

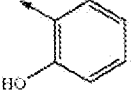
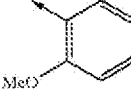
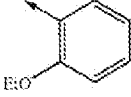
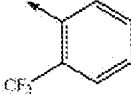
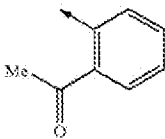
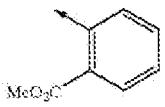
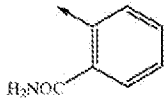
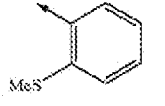
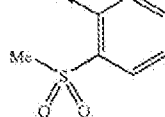
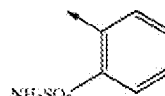
Entry #	Ar ²	MS ES ⁺ (M+)
211		378
212		392
213		406
214		430
215		404
216		420
217		405
218		408
219		440
220		441

TABLE 2-continued

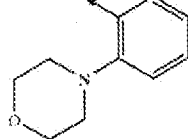
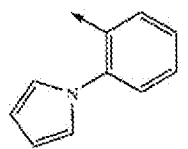
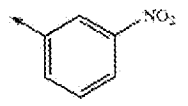
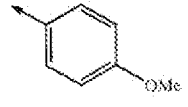
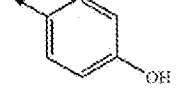
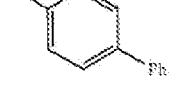
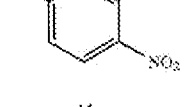
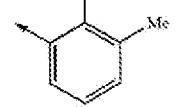
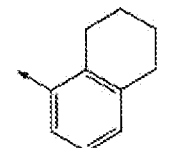
Entry #	Ar ²	MS ES ⁺ (M+)
221		447
222		427
223		407
224		392
225		378
226		438
227		407
228		390
229		416

TABLE 2-continued

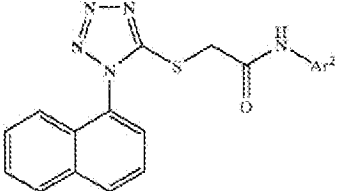
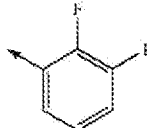
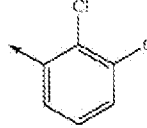
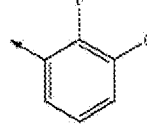
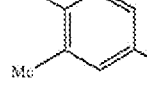
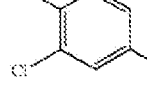
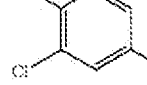
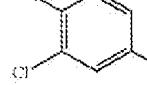
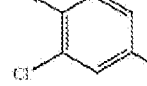
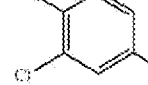
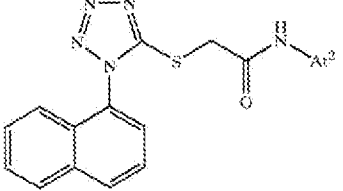
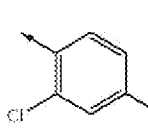
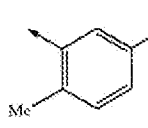
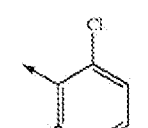
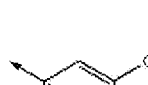
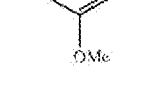
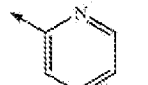
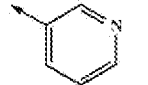
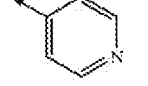
		
Entry #	Ar ²	MS ES ⁺ (M+H)
230		398
231		430/432/434
232		414/416
233		390
234		430/432/434
235		454/456
236		440/442
237		426/428
238		472/474

TABLE 2-continued

		
Entry #	Ar ²	MS ES ⁺ (M+H)
239		419 MS ES ⁺ (M - H)
240		390
241		430/432/434
242		422
243		363
244		363
245		363
246		412/414

[0378]

TABLE 3

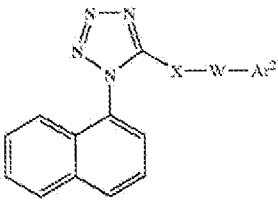
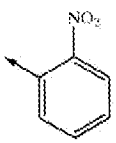
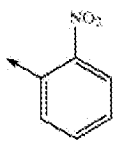
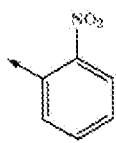
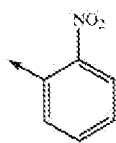
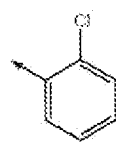
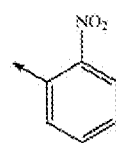
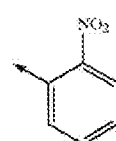
				
Entry #	X	W	Ar ²	MS ES ⁺ (MH)
301	S	CHM&C(O)NH		421
302	O	CH ₂ C(O)NH		391
303	NH	CH ₂ C(O)NH		390
304	CH ₂	CH ₂ C(O)NH		389
305	CH ₂	CH ₂ CH ₂ C(O)NH		392/394
306	CH ₂	CH ₂ CH ₂ C(O)NH		403
307	OH	CHC(O)NH		387

TABLE 3-continued

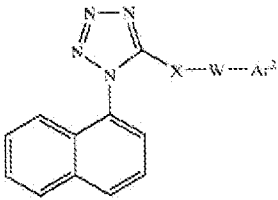
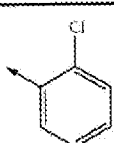
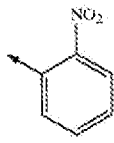
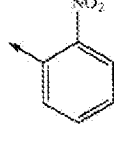
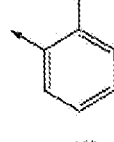
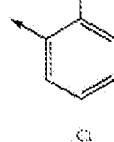
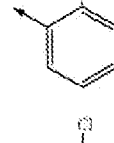
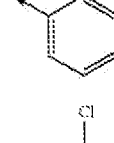

				
Entry #	X	W	Ar ²	MS ES ⁺ (MH)
308	S	CH ₂ C(S)NH		412/414
309	S	CH ₂ CHOH		394
310	S	CH ₂ CH ₂		378
311	S	CH ₂ CH ₂ CH ₂		381/383
312	S	trans-CH ₂ CH=CH		395
313	S	trans-CH ₂ CH=CH		379/381
314	S	trans-CH ₂ CF=CH		397/399
315	S	cis-CH ₂ CF=CH		397/399

TABLE 3-continued

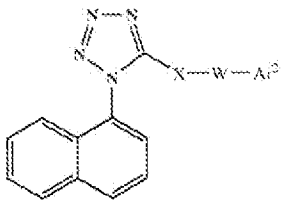
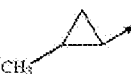
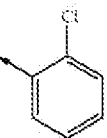
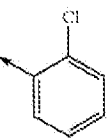
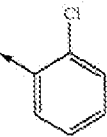
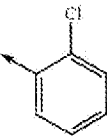
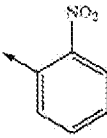
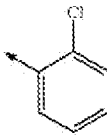
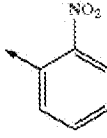
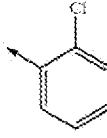
				
Entry #	X	W	Ar ²	MS ES ⁺ (MH)
316	S			393/395
317	S	CH ₂ CH ₂ CHOH		397/399
318	S	CH ₂ CH(OH)CH ₂		397/399
319	S	CH ₂ CH(OH)CHOH		413/415
320	S	CH ₂ CH ₂ O		394
321	S	CH ₂ CH ₂ O		393/395
322	S	CH ₂ CH ₂ O(CO)		422
323	S	CH ₂ CH ₂ O(CO)		411/413

TABLE 3-continued

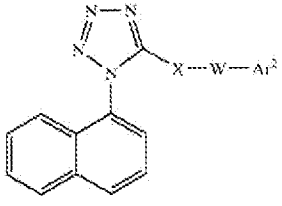
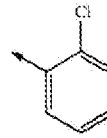
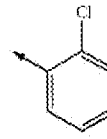
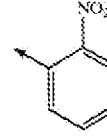
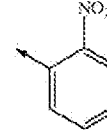
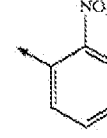
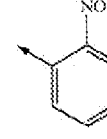
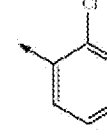
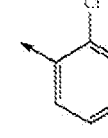
				
Entry #	X	W	Ar ²	MS ES ⁺ (MH)
324	S	CH ₂ CH ₂ CH ₂ O		397/399
325	S	CH ₂ CH(OH)CH ₂ O		413/415
326	S	CH ₂ CH ₂ NH		393
327	S	CH ₂ CH ₂ NMe		407
328	S	CH ₂ CH ₂ NHCH ₃		407
329	S	CH ₂ CH ₂ CH ₂ NH		407
330	S	CH ₂ CH(OH)CH ₂ NH		412/414
331	S	CH ₂ CH ₂ NH(CO)		410/412

TABLE 3-continued

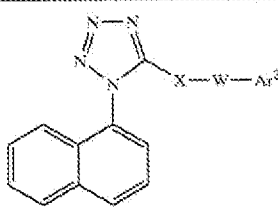
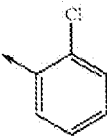
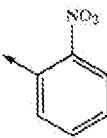
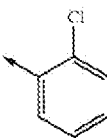
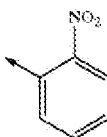
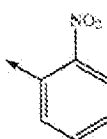
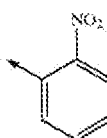
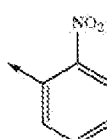
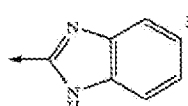
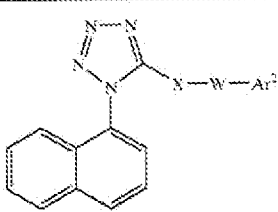
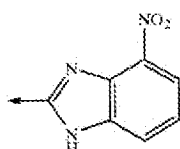
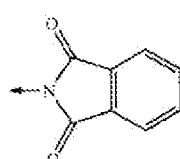
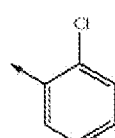
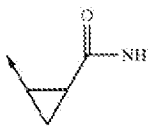
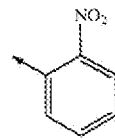
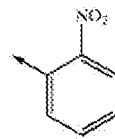
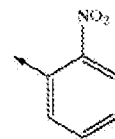
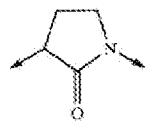
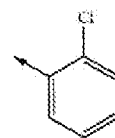
				
Entry #	X	W	Ar ²	MS ES ⁺ (MH)
332	S	CH ₂ CH ₂ NMe(CO)		424/426
333	S	CH ₂ CH ₂ NH(CO)NH		436
334	S	CH ₂ CH ₂ NH(CO)NH		425/427
335	CH ₂	SCH ₂ (CO)NH		421
336	CH ₂	OCH ₂ (CO)NH		405
337	CH ₂	NHCH ₂ (CO)NH		404
338	CH ₂	N(Me)CH ₂ (CO)NH		418
339	S	CH ₂		359

TABLE 3-continued

				
Entry #	X	W	Ar ²	MS ES ⁺ (MH)
340	S	CH ₂		404
341	S	CH ₂ CH ₂		402
342	S	CH ₂ (CO)NMe		410/412
343	---			401
344	S	CH ₂ (CO)NHCH ₂		421
345	S	CH ₂ (CO)CH ₂		406
346	S			422/424

[0379]

TABLE 4

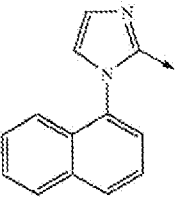
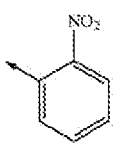
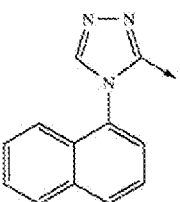
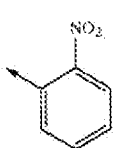
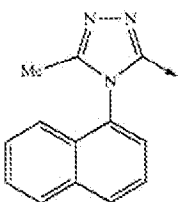
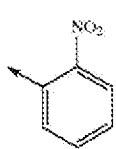
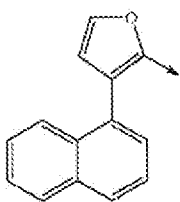
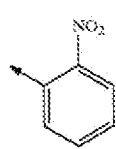
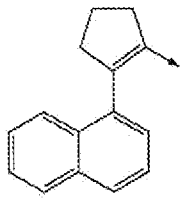
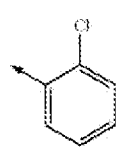
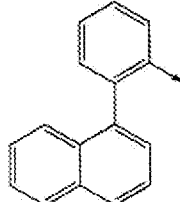
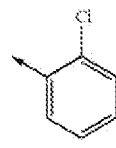
Entry #	Ar ¹	Ar ¹ —X—W—Ar ²			MS ES ⁺ (MH)
		X	W	Ar ²	
401		S	CH ₂ C(O)NH		405
402		S	CH ₂ C(O)NH		406
403		S	CH ₂ C(O)NH		420
404		CH ₂	CH ₂ C(O)NH		387
405		CH ₂	CH ₂ C(O)NH		376/378
406		S	CH ₂ C(O)NH		404/405

TABLE 4-continued

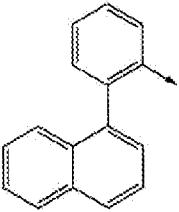
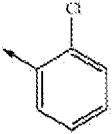
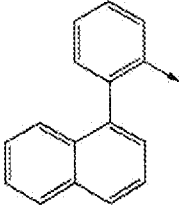
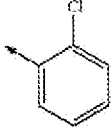
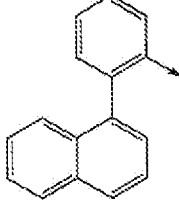
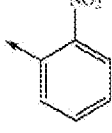
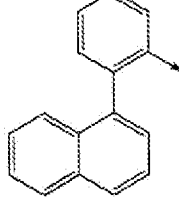
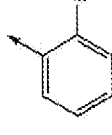
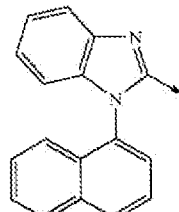
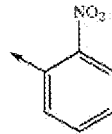
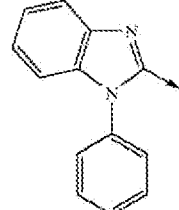
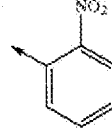
Entry #	Ar^1	$Ar^1-X-W-Ar^2$			MS ES ⁺ (MH)
		X	W	Ar^2	
407		SO	$CH_2C(O)NH$		420/422
408		SO ₂	$CH_2C(O)NH$		436/438
409		O	$CH_2C(O)NH$		399
410		CH ₂	$CH_2C(O)NH$		386/388
411		S	$CH_2C(O)NH$		455
412		S	$CH_2C(O)NH$		405

TABLE 4-continued

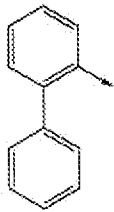
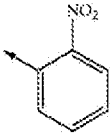
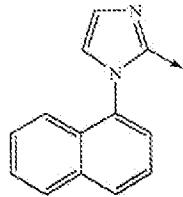
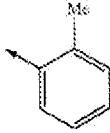
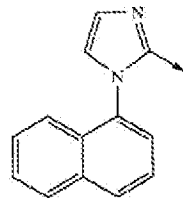
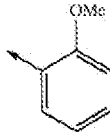
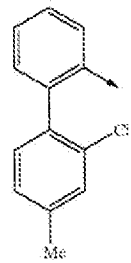
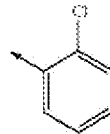
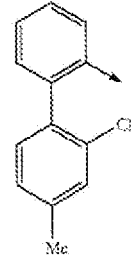
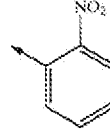
Entry #	Ar ¹	Ar ¹ —X—W—Ar ²		Ar ²	MS ES ⁺ (MH)
		X	W		
413		a	CH ₂ C(O)NH		349
414		S	CH ₂ C(O)NH		374
415		S	CH ₂ C(O)NH		390
416		S	CH ₂ C(O)NH		402/404/406
417		S	CH ₂ C(O)NH		413/415

TABLE 4-continued

Entry #	Ar ¹	Ar ² -X-W-Ar ²		Ar ²	MS ES ⁺ (MH)
		X	W		
418		S	CH ₂ C(O)NH		460/462/464
419		S	CH ₂ C(O)NH		446/448
420		CB ₂	CH ₂ C(O)NH		385/387
421		S	CH ₂ C(O)NH		388/390
422		S	CH ₂ C(O)		345

TABLE 4-continued

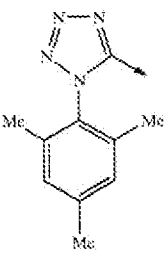
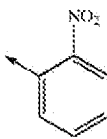
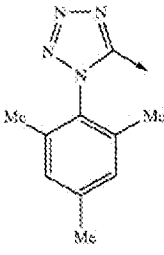
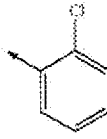
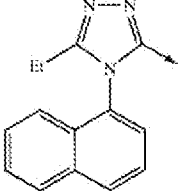
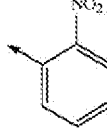
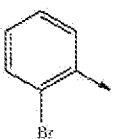
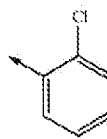
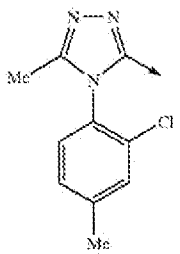
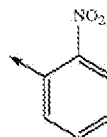
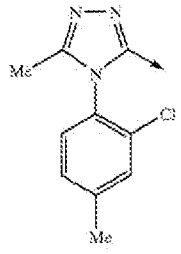
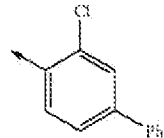
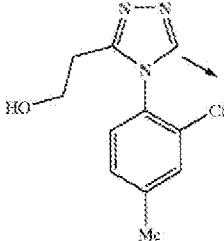
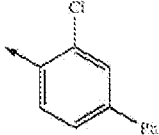
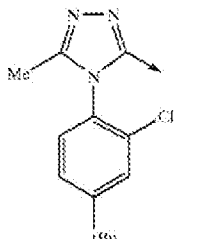
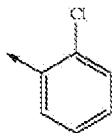
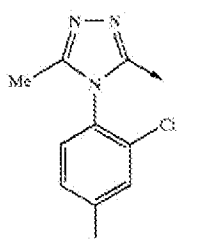
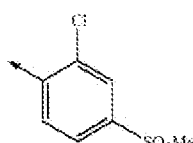
Entry #	Ar ¹	Ar ¹ —X—W—Ar ²			MS ES ⁺ (MH)
		X	W	Ar ²	
423		S	CH ₂ C(O)		383
424		S	CH ₂ C(O)		379
425		S	CH ₂ C(O)NH		434
426		S	CH ₂ C(O)NH		354/356/358 MS ES ⁺ (M - H)
427		S	CH ₂ C(O)NH		418/420
428		S	CH ₂ C(O)NH		483/485/487

TABLE 4-continued

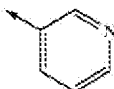
Entry #	Ar^1	$Ar^1 \cdots X \cdots W \cdots Ar^2$			MS ES ⁺ (MH)
		X	W	Ar^2	
429		S	$CH_2C(O)NH$		513/515/517
430		S	$CH_2C(O)NH$		449/451
431		S	$CH_2C(O)NH$		527/529

[0380]

TABLE 5

Entry #	R^9	R^{10}	MS ES ⁺ (MH)
501	Cl	H	354/396/398
502	Cl	Me	408/410/412
503	Cl	CO_2H	438/440/442
504	Cl	$CONH_2$	437/439/441
505	Br	CO_2H	482/484/486
506	NO_2	CO_2Me	463/465
507	NO_2	CO_2H	449/451
508	NO_2	$CONH_2$	448/450
509	Cl	SO_2Me	472/474/476
510	Cl	Ph	470/472/474

TABLE 5-continued

Entry #	R^9	R^{10}	MS ES ⁺ (MH)
511	Me	Ph	450/452
512	Cl		471/473/475

[0381]

TABLE 6

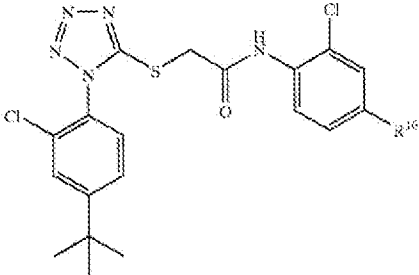

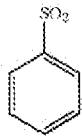

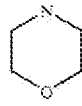


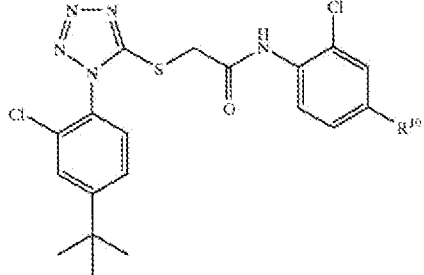

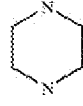
		
Entry #	R ¹⁶	MS ES ⁺ (MH)
601	(CH ₂) ₂ CO ₂ H	508/510/512
602	NO ₂	481/483/485
603	SO ₂ Me	514/516/518
604	SO ₂ NB ₂	515/517/---
605		610/612/614
606		576/578/580
607	SO ₂ CH(Me) ₂	542/544/546
608	SO ₂ CH ₂ CH(Me) ₂	556/558/560
609	SO ₂ CH ₂ CO ₂ H	573/575/---
610		534/536/538
611		521/523/525
612		505/507/509
613		519/521/523

TABLE 6-continued

		
Entry #	R ¹⁶	MS ES ⁺ (MH)
614		620/622/624
615		520/522/524
616	CO ₂ H	480/482/484
617	NH ₂	451/453/455

[0382]

TABLE 7

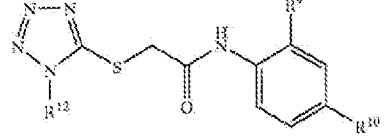
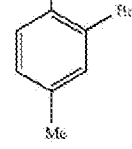
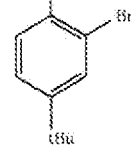
				
Entry #	R ⁹	R ¹⁰	R ¹²	MS ES ⁺ (MH)
701	Cl	H		438/440/442
702	Cl	H		436/438/440

TABLE 7-continued

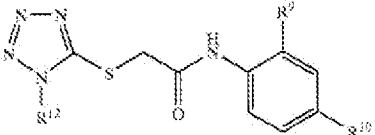
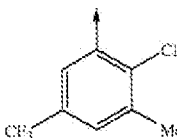
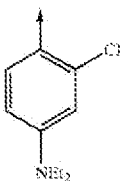
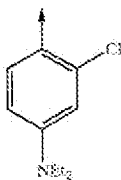
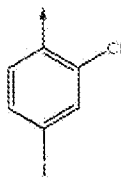
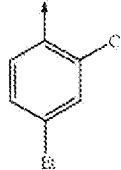
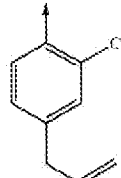
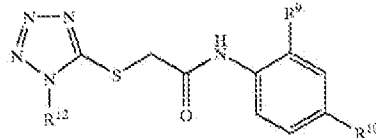
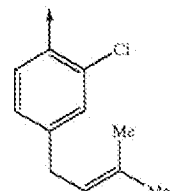
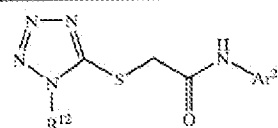
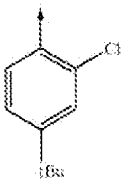
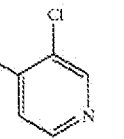
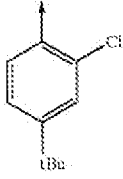
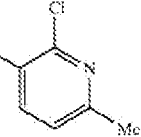
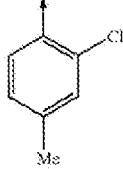
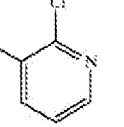
				
Entry #	R ⁹	R ¹⁰	R ¹²	MS ES ⁺ (MH)
703	Cl	SO ₂ NH ₂		541/543/545
704	Me	SO ₂ NH ₂		521/523
705	Cl	H		451/453/455
706	Cl	H		506/508/510
707	Cl	H		408/410/412
708	Cl	H		420/422/424

TABLE 7-continued

				
Entry #	R ⁹	R ¹⁰	R ¹²	MS ES ⁺ (MH)
709	Cl	H		448/450/452

[0383]

TABLE 8

			
Entry #	R ¹²	Ar ²	MS ES ⁺ (MH)
801			437/439/441
802			451/453/455
803			395/397/399

[0384] Reverse Transcriptase (RT) Assays

[0385] Enzymatic Assay (IC₅₀)

[0386] The enzymatic assay employed is described as follows: The reverse transcriptase (RT) enzyme assay has been adapted to a 96-well microtiter plate format and uses PicoGreenTM as a fluorescent intercalator. More explicitly, the HIV-1 RT enzyme was thawed and appropriately diluted

into Tris/HCl 50 mM pH 7.8 containing NaCl 60 mM, $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ 2 mM, DTT 6 mM, GSH 2 mM and 0.02% w/v Chaps to give ≈ 10 nM enzyme. To 10 μL of this enzyme solution was added 10 μL of inhibitor solution (40 μM to 78 nM inhibitor in the same assay buffer as above containing 4% v/v DMSO). The plate was pre-incubated for 1.5 minutes at room temperature before proceeding to the next step. In this pre-incubation step, the highest and lowest inhibitor concentrations were 20 μM and 1.016 nM respectively and the concentration of DMSO was 2% v/v. Then the enzymatic reaction was initiated by addition of 20 μL of substrate solution. The final reaction mixture contained Tris/HCl 50 mM pH 7.8, NaCl 60 mM, $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ 2 mM, DTT 6 mM, GSH 2 mM, CHAPS 0.02% w/v, DMSO 1% v/v, poly rC 45 nM, dG₁₅ 4.5 nM, dGTP 3.6 μM , and ≈ 2.5 nM enzyme. In this incubation step, the highest and lowest inhibitor concentrations were 10 μM and 0.508 nM respectively. After addition of the substrate cocktail, the plate was covered with a plastic seal and incubated for 50 minutes at 37° C. in a dry incubator. The reaction was then quenched by addition of 5 μL of EDTA 0.5 M. The plate was shaken for 30 seconds at medium speed and incubated for 5 minutes at room temperature. Then 160 μL of PicoGreen™ 1:400 dilution from commercial stock (diluted in Tris 20 mM pH 7.5 with EDTA 1 mM) was added and the plate was shaken for 30 seconds and incubated for 10 minutes at room temperature. The plate was then analyzed using a POLARstar Galaxy fluorimeter (BMG Labtechnologies) with λ_{ex} and λ_{em} of 485 nm and 520 nm respectively. Each well was read for 1.25 second. Each row contained at its extremities a blank and a control well.

[0387] P24 Cellular Assay (EC_{50}) (Data Identified with * in Table 9).

[0388] The p24 assay is as described in WO 01/96338, the contents of which are herein incorporated by reference.

[0389] C8166 HIV-1 Luciferase Assay (EC_{50})

[0390] Plasmid: pGL3 Basic LTR/TAR #12

[0391] Plasmid is the pGL3 Basic Vector (a promoterless luciferase expression vector from Promega catalogue #E1751) with the addition of HIV-1 HXB2 LTR sequence from nucleotide -138 to +80 (ScaI-HindIII) upstream of the luciferase gene and the gene for blasticidine resistance cloned in.

[0392] Cells: C8166 LTRluc #A8-F5-G7

[0393] C8166 cells are a human T-lymphotrophic virus type 1 immortalized but nonexpressing line of cord blood lymphocytes and are highly permissive to HIV-1 infection. The reporter cells were made by electroporating C8166 cells with pGL3 Basic LTR/TAR and then selecting positive clones with blasticidine. The clone C8166-LTRluc #A8-F5-G7 was selected by 3 consecutive rounds of limiting dilution under blasticidine selection.

[0394] Media: Complete media consisting of: RPMI 1640+10% FBS+ 10^{-5} M

[0395] β -mercaptoethanol+10 $\mu\text{g}/\text{ml}$ gentamycin. Cultures are maintained in complete media with 5 $\mu\text{g}/\text{ml}$ blasticidine, however, selection is removed for the assay.

[0396] Luciferase Assay Protocol

[0397] Preparation of Compounds

[0398] Serial dilutions of HIV-1 inhibitors compounds are prepared in complete media from 10 mM DMSO stock solutions. Eleven serial dilutions of 2.5 \times are made at 8 \times desired final concentration in a 1 ml deep well titer plate (96 wells). The 12th well contains complete media with no inhibitor and serves as the positive control. All samples contain the same concentration of DMSO ($\leq 0.1\%$ DMSO). A 25 μL aliquot of inhibitor is added, to triplicate wells, of a 96 well tissue culture treated clear view black microtiter plate (Corning Costar catalogue # 3904). The last row is reserved for uninfected C8166 LTRluc cells to serve as the background blank control and the first row is media alone.

[0399] Infection of Cells

[0400] Count C8166 LTRluc cells and place in a minimal volume of complete RPMI 1640 in a tissue culture flask (ex. 30×10^6 cells in 10 ml media/25 cm² flask). Infect cells with HIV-1 at a moi of 0.005. Incubate cells for 1.5 hours at 37° C. on a rotating rack in a 5% CO₂ incubator. Resuspend cells in complete RPMI to give a final concentration of 25,000 cells/175 μL . Add 175 μL of cell mix to wells of 96 well microtiter plate containing 25 μL 8 \times inhibitors. Add 25,000 uninfected C8166-LTRluc cells/well in 200 μL complete RPMI to last row for background control. Incubate cells at 37° C. in 5% CO₂ incubator for 3 days.

[0401] Luciferase Assay

[0402] Add 50 μL Steady Glo (luciferase substrate T_{1/2} ≈ 5 hours Promega catalogue # E2520) to each well of the 96 well plate. Determine the relative light units (RLU) of luciferase using the BMG LUMistar Galaxy luminometer. Plates are read from the bottom for 2 seconds per well with a gain of 240.

[0403] The level of inhibition (% inhibition) of each well containing inhibitor was calculated with the following equation:

$$\% \text{ inhibition} = \left(1 - \frac{\text{RLU} \cdot \text{well} - \text{RLU} \cdot \text{blank}}{\text{RLU} \cdot \text{control} - \text{RLU} \cdot \text{blank}} \right) \times 100$$

[0404] The calculated % inhibition values were then used to determine EC_{50} , slope factor (n) and maximum inhibition (I_{max}) by the non-linear regression routine NLIN procedure of SAS using the following equation:

$$\% \text{ inhibition} = \frac{I_{\text{max}} \times [\text{inhibitor}]^n}{[\text{inhibitor}]^n + \text{IC}_{50}^n}$$

[0405] The results are listed in Table 9 as IC_{50} (nM) and EC_{50} (nM).

[0406] Table legend: A=>100; B=100-50; C=<50; NT=not tested

[0407] According to this invention these compounds are preferred which possess an IC_{50} value against the resistant mutant K103N/Y181C smaller than 50 nM (range C), most preferably an EC_{50} value against the resistant mutant K103N/Y181C smaller than 50 nM (range C).

TABLE 9

Entry #	IC ₅₀ WT	IC ₅₀ K103N/Y181C	EC ₅₀ WT	EC ₅₀ K103N/Y181C
101	C	A	C*	A*
102	C	A	C*	NT
103	C	A	C*	A*
104	C	A	C*	A*
105	C	A	C*	A*
106	A	NT	NT	NT
107	A	NT	NT	NT
108	A	A	NT	NT
109	B	A	C*	A*
110	A	A	NT	NT
111	B	A	C*	A*
112	A	A	NT	NT
113	C	A	C*	NT
114	C	A	C*	A*
115	B	A	C*	A*
116	C	A	C*	NT
117	C	A	NT	A*
118	B	A	C*	A*
119	A	A	NT	NT
120	A	NT	NT	NT
121	A	NT	NT	NT
122	C	A	C*	A*
123	C	A	NT	B*
124	C	A	C*	B*
125	C	A	C*	A*
126	A	A	NT	NT
127	C	A	C*	A*
128	A	A	C*	A*
129	C	A	C*	C*
130	C	A	C*	NT
131	A	NT	NT	NT
132	A	NT	NT	NT
133	C	A	C*	A*
134	C	A	C*	A*
135	C	A	C*	A*
136	B	A	C*	A*
137	A	A	NT	NT
138	A	NT	NT	NT
139	C	A	C*	NT
140	C	A	C*	C*
141	A	A	C*	C*
142	NT	A	C	A
143	NT	A	C	A
144	C	A	NT	NT
145	C	A	C	A
146	C	B	C	B
147	C	A	C	B
201	A	A	NT	NT
202	A	A	NT	NT
203	A	NT	NT	NT
204	A	NT	NT	NT
205	A	NT	NT	NT
206	A	NT	NT	NT
207	A	NT	NT	NT
208	C	NT	C	A
209	C	NT	A*	NT
210	B	NT	C*	A*
211	A	NT	C	A
212	A	NT	NT	NT
213	A	NT	NT	NT
214	A	NT	NT	NT
215	A	NT	NT	NT
216	A	NT	NT	NT
217	A	NT	NT	NT
218	A	NT	NT	NT
219	A	NT	NT	NT
220	A	NT	NT	NT
221	A	NT	NT	NT
222	A	NT	NT	NT
223	A	NT	NT	NT
224	A	NT	NT	NT
225	A	NT	NT	NT
226	A	NT	NT	NT

TABLE 9-continued

Entry #	IC ₅₀ WT	IC ₅₀ K103N/Y181C	EC ₅₀ WT	EC ₅₀ K103N/Y181C
227	A	NT	NT	NT
228	A	NT	NT	NT
229	A	NT	NT	NT
230	B	NT	B*	A*
231	B	NT	C*	A*
232	A	NT	NT	NT
233	A	NT	NT	NT
234	B	NT	B*	A*
235	C	A	C*	NT
236	B	A	A*	A*
237	C	A	C	NT
238	C	A	B	A
239	B	A	C*	A*
240	A	A	NT	NT
241	A	NT	NT	NT
242	A	NT	NT	NT
243	A	NT	NT	NT
244	A	NT	NT	NT
245	A	NT	NT	NT
246	C	A	C	A
301	B	A	C*	A*
302	A	A	B*	NT
303	A	NT	NT	NT
304	A	NT	NT	NT
305	A	NT	NT	NT
306	A	NT	NT	NT
307	A	NT	NT	NT
308	A	NT	B*	NT
309	A	NT	NT	NT
310	A	NT	NT	NT
311	A	NT	NT	NT
312	A	NT	NT	NT
313	A	NT	NT	NT
314	A	NT	NT	NT
315	A	NT	NT	NT
316	B	A	C*	NT
317	B	A	C*	NT
318	B	A	C*	NT
319	A	NT	NT	NT
320	A	NT	NT	NT
321	A	NT	NT	NT
322	A	NT	NT	NT
323	A	NT	NT	NT
324	A	NT	NT	NT
325	A	A	NT	NT
326	A	NT	NT	NT
327	A	NT	NT	NT
328	A	NT	NT	NT
329	A	NT	NT	NT
330	B	A	C*	NT
331	A	NT	NT	NT
332	A	NT	NT	NT
333	A	NT	NT	NT
334	A	NT	NT	NT
335	A	NT	NT	NT
336	A	NT	NT	NT
337	A	NT	NT	NT
338	A	NT	NT	NT
339	A	NT	NT	NT
340	A	NT	NT	NT
341	A	NT	NT	NT
342	A	NT	NT	NT
343	A	NT	NT	NT
344	A	NT	NT	NT
345	A	NT	NT	NT
346	A	NT	NT	NT
401	A	A	C*	NT
402	B	A	C*	A*
403	C	A	C	A
404	A	NT	NT	NT
405	A	NT	NT	NT
406	C	A	A	NT
407	A	NT	NT	NT

TABLE 9-continued

Entry #	IC ₅₀ WT	IC ₅₀ K103N/Y181C	EC ₅₀ WT	EC ₅₀ K103N/Y181C
408	A	NT	NT	NT
409	A	NT	A*	NT
410	A	NT	NT	NT
411	A	A	NT	NT
412	A	NT	NT	NT
413	A	A	NT	NT
414	A	NT	NT	NT
415	A	NT	NT	NT
416	C	A	C	A
417	C	A	C	A
418	C	A	B	NT
419	C	A	B	NT
420	A	NT	NT	NT
421	C	A	C*	A*
422	A	NT	NT	NT
423	A	NT	NT	NT
424	A	NT	NT	NT
425	NT	A	C	A
426	A	NT	NT	NT
427	NT	A	C	A
428	NT	A	C	A
429	C	A	C	A
430	C	B	C	B
431	C	B	C	C
501	C	A	C	A
502	C	A	C	NT
503	C	A	C	A
504	C	A	C	C
505	C	A	C	A
506	C	A	NT	NT
507	C	A	C	A
508	C	B	C	C
509	C	A	C	A
510	C	B	C	A
511	C	A	C	A
512	C	A	C	A
601	C	A	C	A
602	C	A	B	A
603	C	C	C	C
604	C	C	C	C
605	C	A	B	A
606	C	B	C	B
607	C	A	C	B
608	C	A	C	B
609	NT	B	NT	NT
610	C	A	C	A
611	C	A	C	A
612	C	A	B	A
613	C	A	C	A
614	C	A	C	A
615	C	A	C	A
616	C	B	C	C
617	C	A	C	B
701	C	A	NT	NT
702	C	B	C	A
703	C	B	C	C
704	B	A	NT	NT
705	C	A	C	A
706	C	A	C	A
707	C	A	C	A
708	C	A	C	A
709	C	A	A	A
801	C	C	C	C
802	C	A	C	B
803	NT	A	C	A

What is claimed is:

1. A method for treating an HIV infection comprising administering to an infected human a therapeutically effective amount of a compound of formula 1:



wherein Ar¹ is

(i) 5- or 6-membered aromatic heterocycle containing 1 to 4 heteroatoms selected from n, O or S; said heterocycle optionally substituted with (C₁₋₄)alkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₃)alkyl-, wherein said alkyl, cycloalkyl or cycloalkylalkyl may be monosubstituted with —OH; and/or phenyl when the heterocycle contains 1 to 3 n-atoms; in either instance, the said heterocycle is optionally substituted with:

phenyl, phenylmethyl, 5- or 6-membered aromatic heterocycle, fused phenyl-unsaturated or saturated 5- or 6-membered carbocycle, fused phenyl-{unsaturated or saturated 5- or 6-membered carbocycle}methyl, or fused phenyl-5- or 6-membered aromatic heterocycle; each of said phenyl, phenylmethyl, aromatic heterocycle, fused phenyl-carbocycle, fused phenyl-(carbocycle)methyl or fused phenyl-aromatic heterocycle in turn is substituted optionally with 1 to 3 substituents selected independently from:

(C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₃)alkyl, (C₂₋₆)alkenyl, O—(C₁₋₄)alkyl, S—(C₁₋₄)alkyl, halo, CF₃, OCF₃, OH, NO₂, CN, phenyl optionally substituted with C₁₋₆alkyl or nitro, phenylmethyl optionally substituted with C₁₋₆alkyl or nitro, SO₂NH₂, SO₂—(C₁₋₄)alkyl, C(O)NH₂, C(O)OR¹, NR²R³, morpholino or 1-pyrrolyl, wherein R¹ is H or (C₁₋₄)alkyl, and wherein R² and R³ each independently is H or (C₁₋₄)alkyl; wherein said substituents are sterically compatible; or

(ii) unsaturated or saturated 5- or 6-membered carbocycle substituted with phenyl or naphthyl, said unsaturated or saturated carbocycle, or the phenyl or naphthyl optionally substituted with the same 1 to 3 substituents as defined for the substituents in section (i); or

(iii) benzimidazole optionally N-substituted with phenyl or a fused phenyl-carbocycle as defined above;

X is a heteroatom selected from O, S, SO, SO₂ or NR⁴ wherein R⁴ is H or (C₁₋₄)alkyl;

or X is a valence bond or CR^{4A}R^{4B} wherein R^{4A} and R^{4B} each independently is H or (C₁₋₄)alkyl; and

when X is a heteroatom, including NR⁴;

W is a divalent radical selected from:

(a) (CR⁵R^{5A})_{1,2}—C(Z^A)NR⁶ wherein R⁵ and R^{5A} each independently is H or (C₁₋₄)alkyl, R⁶ is H or (C₁₋₄)alkyl, and Z^A is oxo or thioxo;

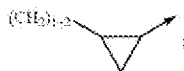
(b) D-C(Z^B) wherein D is (C₁₋₄)alkylene, (C₁₋₄)alkylene-O or (C₁₋₄)alkylene-NR⁷ wherein R⁷ is H or (C₁₋₄)alkyl, and Z^B is oxo or thioxo;

(c) CH₂C(Z^C)NR^{7A}(C₁₋₄)alkylene wherein Z^C is oxo or thioxo and R^{7A} is H or (C₁₋₄)alkyl;

(d) (C₁₋₄)alkylene-NR^{7B}C(Z^D)NR^{7C} wherein R^{7B} and R^{7C} each independently is H or (C₁₋₄)alkyl, and Z^D is oxo or thioxo;

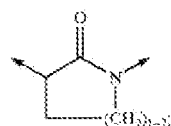
(e) (C₁₋₄)alkylene optionally substituted with OH, or optionally disubstituted with OH when the (C₁₋₄)alkylene contains 2 to 4 carbon atoms; (C₂₋₄)alkenyl optionally substituted with halo; or

cis- or trans-



or

- (f) $\{(C_{1-4})\text{alkylene}\}-O$ optionally substituted on the alkylene portion with OH;
- (g) $\{(C_{1-4})\text{alkylene}\}-NR^6$ optionally substituted on the alkylene portion with OH, and R^6 is H or $(C_{1-4})\text{alkyl}$;
- (h) $(C_{1-4})\text{alkylene}-C(Z^B)(C_{1-4})\text{alkylene}$ wherein Z^B is oxo or thioxo; or
- (i)



or

- (j) $(CR^{5A}R^{5A})_{1,2}-NR^6-(CR^{5A}R^{5A})_{1,2}$ wherein R^5 and R^{5A} each independently is H or $(C_{1-4})\text{alkyl}$, R^6 is H or $(C_{1-4})\text{alkyl}$; or

when X is a valence bond:

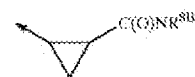
W is a $\{(C_{2-4})\text{alkenyl}\}C(O)NR^{8A}$,

cis- or trans-



or

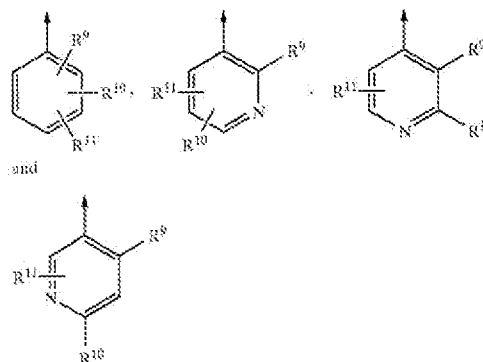
cis- or trans-

wherein R^{8A} and R^{8B} each is H or $(C_{1-4})\text{alkyl}$; orwhen X is $CR^{4A}R^{4B}$ as defined above:

W is selected from $\{(C_{1-4})\text{alkylene}\}C(O)NR^{8C}$, $S-\{(C_{1-4})\text{alkylene}\}C(O)NR^{8D}$, $O-\{(C_{1-4})\text{alkylene}\}C(O)NR^{8E}$, or $NR^{8F}-\{(C_{1-4})\text{alkylene}\}-NR^{8G}$ wherein R^{8C} , R^{8D} , R^{8E} , R^{8F} and R^{8G} each independently is H or $(C_{1-4})\text{alkyl}$; and

 Ar^2 is

- (i) a phenyl or pyridinyl selected from the formulas

wherein R^9 , R^{10} and R^{11} each independently represents:

H, $(C_{1-6})\text{alkyl}$, $(C_{2-7})\text{cycloalkyl}$, $(C_{3-7})\text{cycloalkyl}$, $(C_{1-3})\text{alkyl}$, $(C_{2-6})\text{alkenyl}$, $O-(C_{1-6})\text{alkyl}$, $S-(C_{1-6})\text{alkyl}$, halo, CF_3 , OCF_3 , OH, NO_2 , CN, $-NR^{N1}R^{N2}$, $-C(O)R^{21}$, $-(C_{1-3})\text{alkyl}-C(O)R^{21}$, $-C(O)OR^{22}$, $-(C_{1-3})\text{alkyl}-C(O)OR^{22}$, $-SO_2-$, $(C_{1-3})\text{alkyl}-C(O)OR^{22}$, wherein R^{21} is $(C_{1-4})\text{alkyl}$; R^{22} is H or $(C_{1-4})\text{alkyl}$; $C(O)NH_2$, $-(C_{1-3})\text{alkyl}-C(O)NH_2$,

 $S(O)-(C_{1-4})\text{alkyl}$, $SO_2-(C_{1-4})\text{alkyl}$, SO_2NH_2 ,

phenyl, phenylmethyl, phenyl- SO_2- , 2-, 3- or 4-pyridinyl, 1-pyrrolyl, whereby said phenyl, pyridinyl and pyrrolyl may have one or more substituents selected from the group consisting of halo, NO_2 , C_{1-3} -alkyl and CF_3 ;

wherein the substituents R^9 , R^{10} and R^{11} are sterically compatible;

wherein R^{N1} , R^{N2} each independently represent H or $(C_{1-6})\text{alkyl}$, whereby R^{N1} and R^{N2} may be covalently bonded to each other to form together with the N-atom to which they are attached to a 4 to 7-membered heterocycle whereby the $-CH_2-$ group at the position 4 of a 6 or 7-membered heterocycle may be replaced by $-O-$, $-S-$ or $-NR^{N3}$ wherein R^{N3} represents H, $-C(O)OR^{22}$, $(C_{1-6})\text{alkyl}$, $(C_{3-7})\text{cycloalkyl}$ or $(C_{3-7})\text{cycloalkyl}-(C_{1-3})\text{alkyl}$, wherein R^{22} is H or $(C_{1-4})\text{alkyl}$; or

- (ii) Ar^2 is a fused phenyl-(saturated or unsaturated 5- or 6-membered carbocyclic ring optionally substituted with 1 to 3 substituents selected independently from $(C_{1-4})\text{alkyl}$, $O-(C_{1-4})\text{alkyl}$, $S-(C_{1-4})\text{alkyl}$, NO_2 or halo; or

- (iii) Ar^2 is a 5- or 6-membered aromatic heterocycle containing 1 to 4 heteroatoms selected from N, O or S, or a fused phenyl-5- or 6-membered heterocycle, said aromatic heterocycle or fused phenyl-heterocycle is optionally substituted with 1 to 3 substituents selected independently from $(C_{1-4})\text{alkyl}$, $O-(C_{1-4})\text{alkyl}$, $S-(C_{1-4})\text{alkyl}$, NO_2 or halo; or

- (iv) Ar^2 is phthalimido and W is $(C_{1-4})\text{alkylene}$; or a pharmaceutically acceptable salt thereof.

2. A method according to claim 1, wherein Ar^1 is

- (i) 5- or 6-membered aromatic heterocycle containing 1 to 4 heteroatoms selected from N, O or S; said heterocycle optionally substituted with (C_{1-4}) alkyl or phenyl when the heterocycle contains 1 to 3 N-atoms; in either instance, the said heterocycle is optionally substituted with:

phenyl, phenylmethyl, 5- or 6-membered aromatic heterocycle, fused phenyl-unsaturated or saturated 5- or 6-membered carbocycle, fused phenyl-{unsaturated or saturated 5- or 6-membered carbocycle}methyl, or fused phenyl-5- or 6-membered aromatic heterocycle; each of said phenyl, carbocycle or heterocycle, in turn is substituted optionally with 1 to 3 substituents selected independently from:

(C_{1-4}) alkyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, halo, CF_3 , OH, NO_2 , CN, phenyl optionally substituted with (C_{1-4}) alkyl, SO_2NH_2 , $SO_2-(C_{1-4})$ alkyl, $C(O)OR$ wherein R^1 is H or (C_{1-4}) alkyl, or NR^2R^3 wherein R^2 and R^3 each independently is H or (C_{1-4}) alkyl; wherein said substituents are sterically compatible; or

- (ii) unsaturated or saturated 5- or 6-membered carbocycle substituted with phenyl or naphthyl, said unsaturated or saturated carbocyclic, or the phenyl or naphthyl optionally substituted with the same 1 to 3 substituents as defined for the substituents in section (i); or

- (iii) benzimidazole optionally N-substituted with phenyl or a fused phenyl-carbocycle as defined above;

X is a heteroatom selected from O, S or NR^4 wherein R^4 is H or (C_{1-4}) alkyl; or X is a valence bond or $CR^{4A}R^{4B}$ wherein R^{4A} and R^{4B} each independently is H or (C_{1-4}) alkyl; and

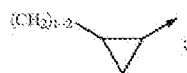
when X is a heteroatom:

W is a divalent radical selected from:

- (a) $(CR^{5A}R^{5B})_{1-2}-C(Z^A)NR^6$ wherein R^5 and R^{5A} each independently is H or (C_{1-4}) alkyl, R^6 is H or (C_{1-4}) alkyl, and Z^A is oxo or thioxo;
- (b) $D-C(Z^B)$ wherein D is (C_{1-4}) alkylene, (C_{1-4}) alkylene-O or (C_{1-4}) alkylene- NR^7 wherein R^7 is H or (C_{1-4}) alkyl, and Z^B is oxo or thioxo;
- (c) $CH_2C(Z^C)NR^{7A}-(C_{1-4})$ alkylene wherein Z^C is oxo or thioxo and R^{7A} is H or (C_{1-4}) alkyl;
- (d) (C_{1-4}) alkylene- $NR^{7B}C(Z^D)NR^{7C}$ wherein R^{7B} and R^{7C} each independently is H or (C_{1-4}) alkyl, and Z^D is oxo or thioxo;

- (e) (C_{1-4}) alkylene optionally substituted with OH, or optionally disubstituted with OH when the (C_{1-4}) alkylene contains 2 to 4 carbon atoms; (C_{2-4}) alkenyl optionally substituted with halo; or

cis- or trans-



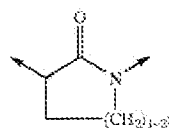
or

- (f) $\{(C_{1-4})$ alkylene $\}-O$ optionally substituted on the alkylene portion with OH;

- (g) $\{(C_{1-4})$ alkylene $\}-NR^8$ optionally substituted on the alkylene portion with OH, and R^8 is H or (C_{1-4}) alkyl;

- (h) (C_{1-4}) alkylene- $C(Z^E)(C_{1-4})$ alkylene wherein Z^E is oxo or thioxo; or

(i)



or

when X is a valence bond:

W is a $\{(C_{2-4})$ alkenyl $\}C(O)NR^{8A}$,

cis- or trans-



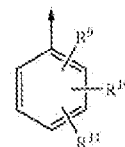
wherein R^{8A} and R^{8B} each is H or (C_{1-4}) alkyl; or

when X is $CR^{4A}R^{4B}$ as defined above:

W is selected from $\{(C_{1-4})$ alkylene $\}C(O)NR^{8C}$, $S-\{(C_{1-4})$ alkylene $\}C(O)NR^{8D}$, $O-\{(C_{1-4})$ alkylene $\}C(O)NR^{8E}$, or $NR^{8F}-\{(C_{1-4})$ alkylene $\}-NR^{8G}$ wherein R^{8C} , R^{8D} , R^{8E} , R^{8F} and R^{8G} each independently is H or (C_{1-4}) alkyl; and

Ar^2 is

- (i) a phenyl of formula



wherein R^9 , R^{10} and R^{11} each independently represents:

H, (C_{1-4}) alkyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, halo, CF_3 , OH, NO_2 , phenyl, phenylmethyl, (2-nitrophenyl)methyl, 2-methylphenyl, $-C(O)-(C_{1-4})$ alkyl, $C(O)NH_2$, $S(O)-(C_{1-4})$ alkyl, SO_2NH_2 , 2-, 3- or 4-pyridinyl, morpholino or 1-pyrrolyl, or $-C(O)OR^{22}$, wherein R^{22} is H or (C_{1-4}) alkyl; wherein the substituents R^9 , R^{10} and R^{11} are sterically compatible; or

- (ii) Ar^2 is a fused phenyl-(saturated or unsaturated 5- or 6-membered carbocyclic ring optionally substituted

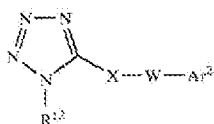
with 1 to 3 substituents selected independently from (C_{1-4}) alkyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, NO_2 or halo; or

(iii) Ar^2 is a 5- or 6-membered aromatic heterocycle containing 1 to 4 heteroatoms selected from N, O or S, or a fused phenyl-5- or 6-membered heterocycle, said aromatic heterocycle or fused phenyl-heterocycle is optionally substituted with 1 to 3 substituents selected independently from (C_{1-4}) alkyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, NO_2 or halo; or

(iv) Ar^2 is phthalimido and W is (C_{1-4}) alkylene;

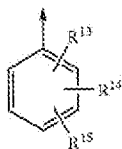
or a pharmaceutically acceptable salt thereof.

3. A method according to claim 2 for treating HIV infections comprising administering to a human infected with HIV a therapeutically effective amount of a compound represented by formula 1a:



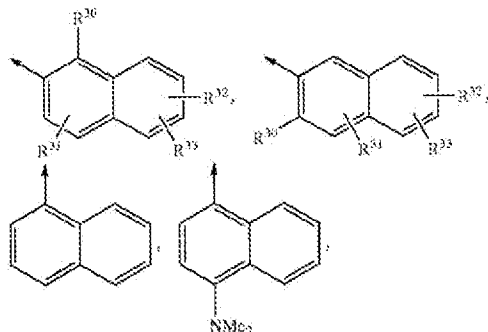
1a

wherein X, W and Ar^2 are as defined in claim 2 and R^{12} is a phenyl of formula



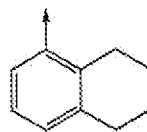
wherein R^{13} , R^{14} and R^{15} each independently represents H, (C_{1-4}) alkyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl- (C_{1-3}) alkyl, (C_{2-6}) alkenyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, halo, CF_3 , OCF_3 , OH, NO_2 , CN, phenyl, 2-methylphenyl, SO_2NH_2 , $SO_2-(C_{1-4})$ alkyl, $C(O)NH_2$, morpholino, 1-pyrrolyl, (2-nitrophenyl)- CH_2 , phenylethyl, $C(O)OR^{16}$ wherein R^{16} is H or (C_{1-4}) alkyl; or

wherein R^{12} is selected from the group consisting of



-continued

and

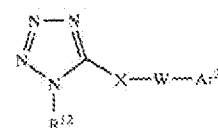


R^{31} , R^{32} ,

R^{33} are each independently selected from the group consisting of H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl- (C_{1-3}) alkyl, (C_{2-6}) alkenyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, halo, CF_3 , OCF_3 , OH, NO_2 , CN, SO_2NH_2 , $SO_2-(C_{1-4})$ alkyl, $C(O)OR^1$ wherein R^1 is H or (C_{1-4}) alkyl, or NR^2R^3 wherein R^2 and R^3 each independently is H or (C_{1-4}) alkyl; and

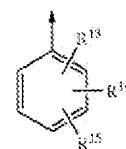
R^{30} represents H, Cl, Br, $COO(C_{1-4})$ alkyl.

4. A method according to claim 2 wherein the compound is a compound of formula 1a



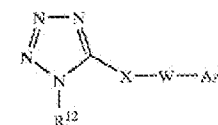
1a

wherein R^{12} is a phenyl of formula



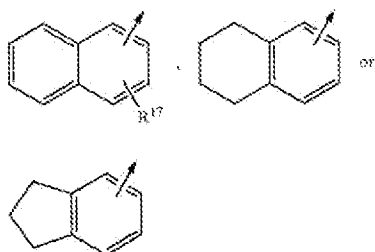
wherein R^{13} , R^{14} and R^{15} each independently represents H, Me, Et, Pr, iPr, tBu, OMe, OEt, OiPr, SMe, SEt, Br, Cl, F, CF_3 , OCF_3 , NO_2 , $C(O)OH$, $C(O)OMe$ or $C(O)OEt$, provided that at least one of R^{13} , R^{14} and R^{15} is other than hydrogen.

5. A method according to claim 2 wherein the compound is a compound of formula 1a



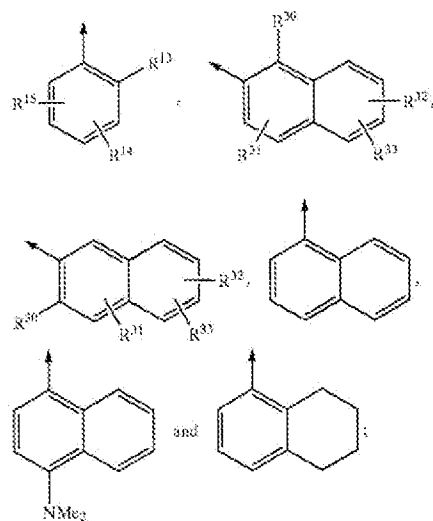
1a

wherein R^{12} is



wherein R^{17} is selected from H, Me, OMe, Cl, F, CF_3 , NH_2 , $NHMe$ or NMe_2 .

6. A method according to claim 3 wherein the compound is a compound of formula 1a wherein R^{12} is selected from:



wherein

R^{13} represents F, Cl, Br, CH_3 , $COO(C_{1-4})alkyl$ and

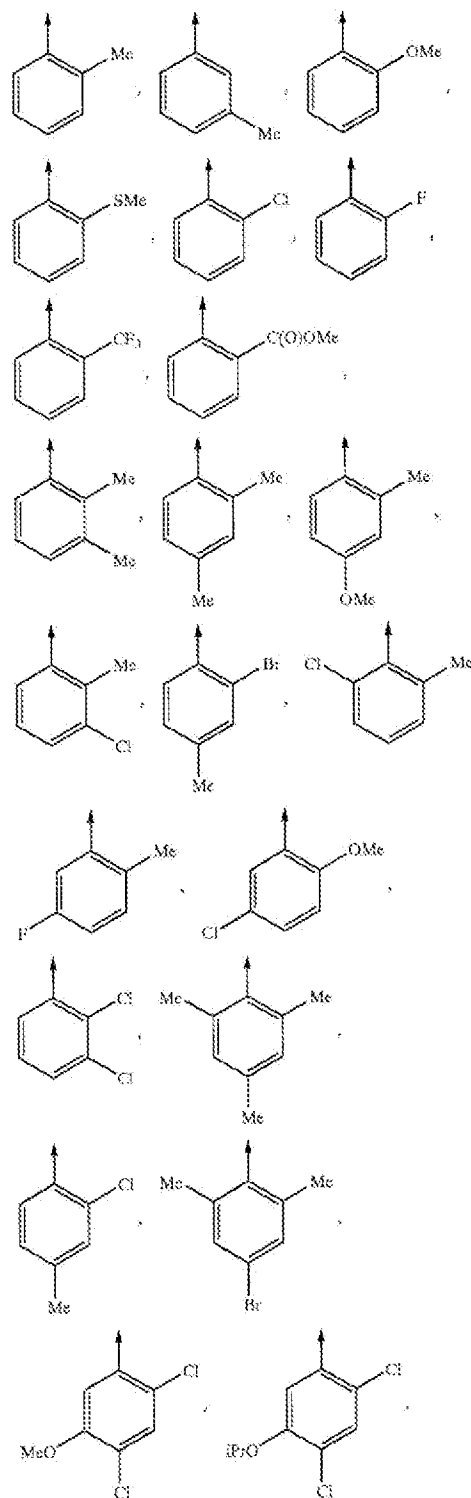
R^{14} , R^{15} ,

R^{31} , R^{32} ,

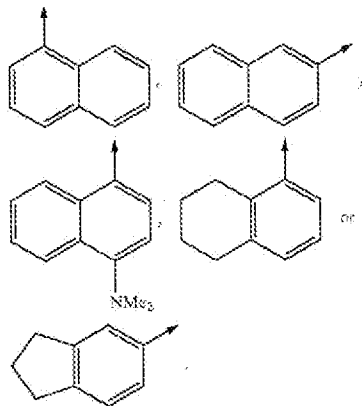
R^{33} are each independently selected from the group consisting of H, $(C_{1-6})alkyl$, $(C_{3-7})cycloalkyl$, $(C_{3-7})cycloalkyl-(C_{1-3})alkyl$, $(C_{2-6})alkenyl$, $O-(C_{1-4})alkyl$, $S-(C_{1-4})alkyl$, halo, CF_3 , OCF_3 , OH, NO_2 , CN, SO_2NH_2 , $SO_2-(C_{1-4})alkyl$, $C(O)OR^1$ wherein R^1 is H or $(C_{1-4})alkyl$, or NR^2R^3 wherein R^2 and R^3 each independently is H or $(C_{1-4})alkyl$; and

R^{30} represents H, Cl, Br, $COO(C_{1-4})alkyl$.

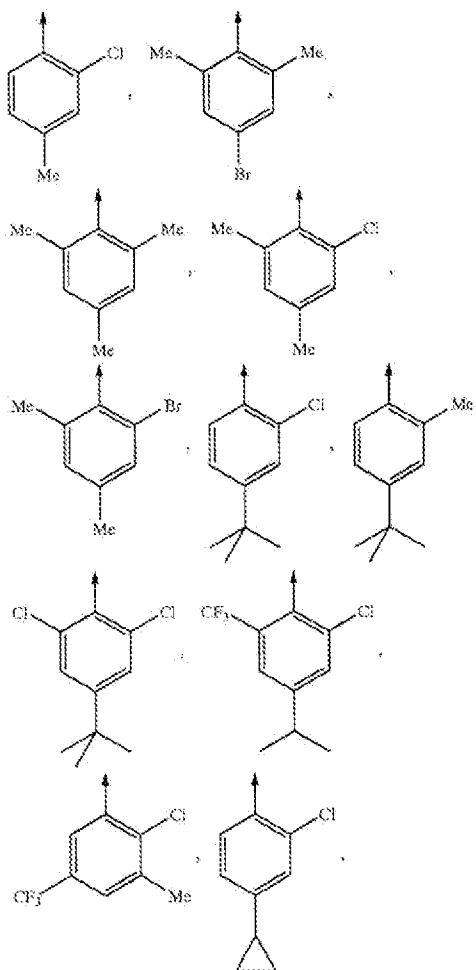
7. A method according to claim 6 wherein the compound is a compound of formula 1a wherein R^{12} is selected from:



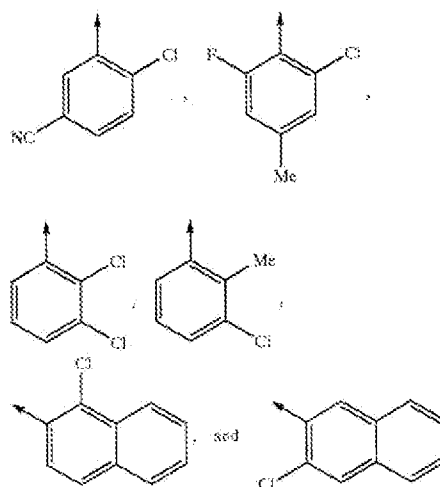
-continued



8. A method according to claim 6 wherein the compound is a compound of formula 1a wherein R^{12} is selected from the group consisting of:



-continued

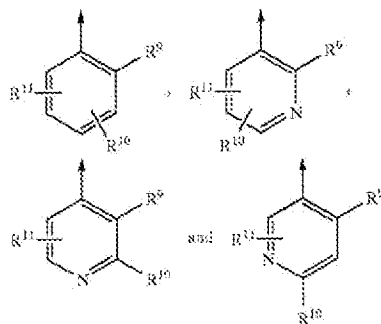


9. A method according to claim 1 wherein the compound is a compound of formula 1 wherein X is O or S.

10. A method according to claim 1 wherein the compound is a compound of formula 1 wherein W is a divalent radical selected from the group consisting of: $-S-(CR^5R^{5A})-$, $-CO-NR^6-$, $-O-(CR^5R^{5A})-CO-NR^6-$, $-S-(C_{2-4}alkylene-O)-$ and $-S-(C_{2-4}alkylene-NR^6)-$, wherein R^5 and R^{5A} each independently is H or $(C_{1-4}alkyl)$, R^6 is H or $(C_{1-4}alkyl)$; and wherein the $(C_{2-4}alkylene)$ group is optionally substituted with OH.

11. A method according to claim 1 wherein the compound is a compound of formula 1 wherein W is $CH(R^5)C(O)NH$ wherein R^5 is H or Me.

12. A method according to claim 1 wherein Ar^2 is selected from the group consisting of



wherein R^9 is $(C_{1-3}alkyl)$, halo or NO_2 .

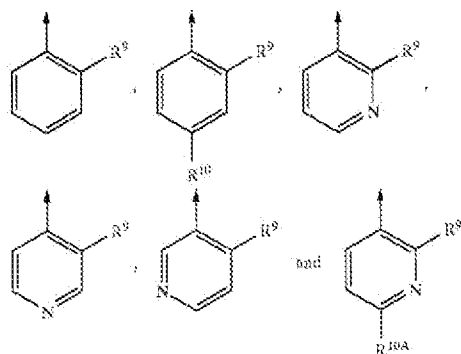
R^{10} , R^{11} are independently of each other selected from the group consisting of H, $(C_{1-6}alkyl)$, $(C_{3-7}cycloalkyl)$, $(C_{3-7}cycloalkyl)-(C_{1-3}alkyl)$, $(C_{2-6}alkenyl)$, $O(C_{1-6}alkyl)$, $S(C_{1-6}alkyl)$, halo, CF_3 , OCF_3 , OH, NO_2 , CN, $-NR^{N1}R^{N2}$, $-C(O)R^{21}$, $-(C_{1-3}alkyl)-C(O)R^{21}$, $-C(O)OR^{22}$, $-(C_{1-3}alkyl)-C(O)OR^{22}$, $-SO_2-(C_{1-3}alkyl)-C(O)OR^{22}$, $-(C_{1-3}alkyl)-C(O)NH_2$, $C(O)NH_2$.

—S(O)—(C₁₋₆)alkyl, —SO₂—(C₁₋₆)alkyl, —SO₂—phenyl, —SO₂—NH₂, phenyl, phenylmethyl, 2-, 3- or 4-pyridinyl, 1-pyrrolyl, whereby said phenyl, pyridinyl and pyrrolyl may have one or more substituents selected from the group consisting of halo, NO₂, C₁₋₃-alkyl and CF₃;

wherein R²¹ is (C₁₋₄)alkyl and R²² is H or (C₁₋₄)alkyl; and

wherein R^{N1}, R^{N2} each independently represent H or (C₁₋₆)alkyl, whereby R^{N1} and R^{N2} may be covalently bonded to each other to form together with the N-atom to which they are attached to a 4 to 7-membered heterocycle whereby the —CH₂—group at the position 4 of a 6 or 7-membered heterocycle may be replaced by —O—, —S— or —NR^{N3}—wherein R^{N3} represents H, —C(O)OR²², (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₃₋₇)cycloalkyl-(C₁₋₃)alkyl, wherein R²² is H or (C₁₋₄)alkyl.

13. A method according to claim 12 wherein Ar² is selected from the group consisting of



wherein R⁹ is C₁ or NO₂;

R^{10A} is (C₁₋₄)alkyl; and

R¹⁰ is selected from the group consisting of (C₁₋₄)alkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₃)alkyl, (C₂₋₆)alkenyl, O(C₁₋₄)alkyl, S(C₁₋₄)alkyl, halo, CF₃, OCF₃, OH, NO₂, CN, —NR^{N1}R^{N2}, —C(O)R²¹, —(C₁₋₃)alkyl-C(O)R²¹, —C(O)OR²², —(C₁₋₃)alkyl-C(O)OR²², —SO₂—(C₁₋₃)alkyl-C(O)OR²², —(C₁₋₃)alkyl-C(O)NH₂, C(O)NH₂, —S(O)—(C₁₋₆)alkyl, —SO₂—(C₁₋₆)alkyl, —SO₂—phenyl, —SO₂—NH₂, phenyl, phenylmethyl, phenyl-SO₂—, 2-, 3- or 4-pyridinyl, 1-pyrrolyl, whereby said phenyl, pyridinyl and pyrrolyl may have one or more substituents selected from the group consisting of halo, NO₂, C₁₋₃-alkyl and CF₃;

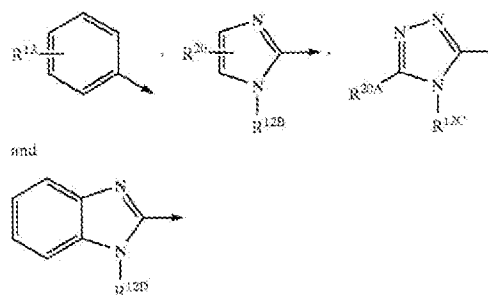
wherein R²¹ is (C₁₋₄)alkyl; and R²² is H or (C₁₋₄)alkyl;

wherein R^{N1}, R^{N2} each independently represent H or (C₁₋₆)alkyl, whereby R^{N1} and R^{N2} may be covalently bonded to each other to form together with the N-atom to which they are attached to a 4 to 7-membered heterocycle whereby the —CH₂—group at the position 4 of a 6 or 7-membered heterocycle may be replaced by —O—, —S— or —NR^{N3}—wherein R^{N3} represents H, —C(O)OR²², (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₃₋₇)cycloalkyl-(C₁₋₃)alkyl, wherein R²² is H or (C₁₋₄)alkyl.

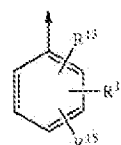
14. A method according to claim 1 for treating HIV infections comprising administering to a human infected with HIV, a therapeutically effective amount of a compound, represented by 1b:



wherein X, W and Ar² are as defined in claim 1 and Ar³ is selected from the group consisting of:

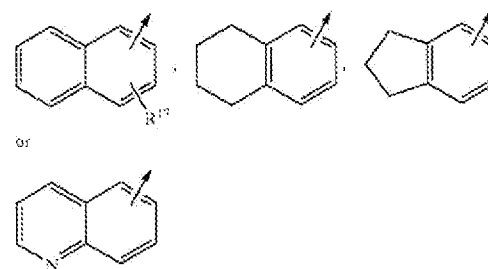


wherein R^{12A}, R^{12B}, R^{12C} and R^{12D} each is a phenyl of formula



wherein R¹³, R¹⁴ and R¹⁵ each independently represents H, (C₁₋₄)alkyl, O—(C₁₋₄)alkyl, S—(C₁₋₄)alkyl, halo, CF₃, OH, NO₂, CN, Ph, 2-methylphenyl, SO₂NH₂, SO₂—(C₁₋₄)alkyl, C(O)NH₂, morpholine, 1-pyrrolyl, (2-NO₂-Ph)CH₂, PhCH₂, C(O)OR¹⁶ wherein R¹⁶ is H or (C₁₋₄)alkyl; or

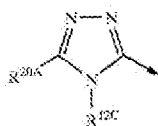
R^{12A}, R^{12B}, R^{12C} and R^{12D} each is



wherein R¹⁷ is H, (C₁₋₄)alkyl, O—(C₁₋₄)alkyl, halo, CF₃ or NR¹⁸R¹⁹ wherein R¹⁸ and R¹⁹ each independently is H or (C₁₋₄)alkyl;

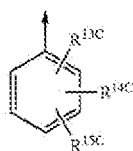
and R²⁰ and R^{20A} each is H or (C₁₋₄)alkyl.

15. A method according to claim 14 wherein the compound is a compound of formula 1b wherein Ar^3 is

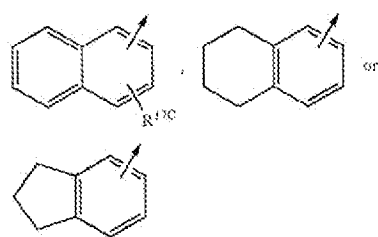


wherein R^{12C} is as defined in claim 14, and R^{20A} is H, Me, Et, Pr or iPr.

16. A method according to claim 15 wherein the compound is a compound of formula 1b wherein R^{12C} is a phenyl of formula



wherein R^{13C} , R^{14C} and R^{15C} each independently is H, Me, Et, Pr, iPr, OMe, OEt, SMe, SEt, Br, Cl, F, CF_3 , NO_2 , $C(O)OH$, $C(O)OMe$ or $C(O)OEt$, provided that at least one of R^{13C} , R^{14C} and R^{15C} is other than hydrogen, and R^{20A} is H, Me or Et; or R^{12C} is

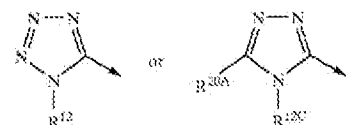


wherein R^{17C} is selected from H, Me, OMe, Cl, F, CF_3 , NH_2 , $NHMe$ or NMe_2 ; and R^{20A} is H, Me or Et.

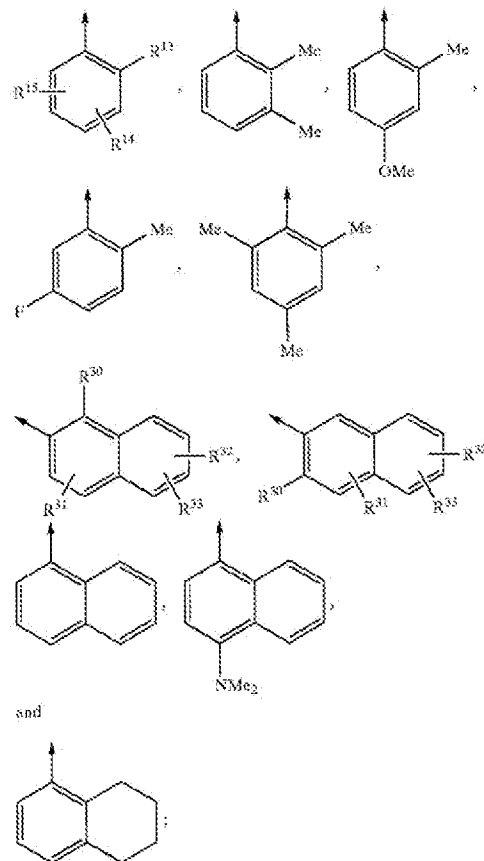
17. A compound of formula 1:



wherein Ar^1 is



wherein R^{12} is selected from the group consisting of



R^{13} represents Cl, Br, $COO(C_{1-4})alkyl$ and

if R^9 is NO_2 , Cl or Br, then R^{13} may also represent F or CH_3 .

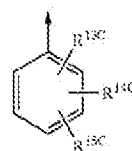
R^{14} , R^{15} ,

R^{31} , R^{32} ,

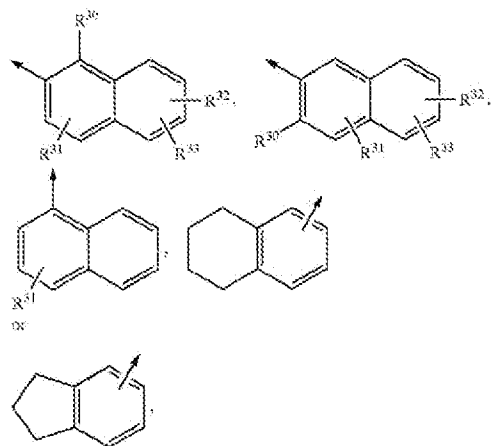
R^{33} are each independently selected from the group consisting of H, $(C_{1-6})alkyl$, $(C_{3-7})cycloalkyl$, $(C_{3-7})cycloalkyl-(C_{1-3})alkyl$, $(C_{2-6})alkenyl$, $O-(C_{1-4})alkyl$, $S-(C_{1-4})alkyl$, halo, CF_3 , OCF_3 , OH, NO_2 , CN, SO_2NH_2 , $SO_2-(C_{1-4})alkyl$, $C(O)OR^1$ wherein R^1 is H or $(C_{1-6})alkyl$, or NR^2R^3 wherein R^2 and R^3 each independently is H or $(C_{1-4})alkyl$;

R^{30} represents H, Cl, Br, $COO(C_{1-4})alkyl$;

R^{12C} is a phenyl of formula



wherein R^{13C} , R^{14C} and R^{15C} each independently represents H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl- (C_{1-3}) alkyl, (C_{2-6}) alkenyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, halo, CF_3 , OCF_3 , OH, NO_2 , CN, SO_2NH_2 , $SO_2-(C_{1-4})$ alkyl, $C(O)OR^1$ wherein R^1 is H or (C_{1-4}) alkyl, or NR^2R^3 wherein R^2 and R^3 each independently is H or (C_{1-4}) alkyl; provided that at least one of R^{13C} , R^{14C} and R^{15C} is other than hydrogen; or R^{12C} is



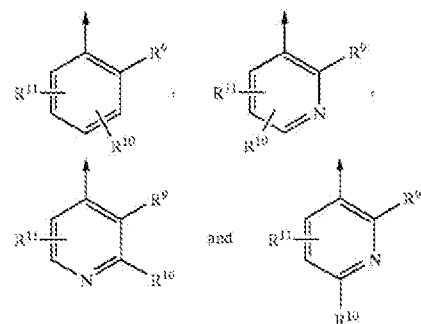
wherein R^{30} , R^{31} , R^{32} , R^{33} are as defined hereinbefore; and

R^{20A} is H, (C_{1-4}) alkyl, (C_{3-7}) cycloalkyl or (C_{3-7}) cycloalkyl- (C_{1-3}) alkyl, wherein said alkyl, cycloalkyl or cycloalkylalkyl may be monosubstituted with $-OH$; and

X is S or O;

W is $CH_2C(O)NR^6$ wherein R^6 is H or (C_{1-4}) alkyl; and

Ar^2 is selected from the group consisting of



wherein R^9 is halo or NO_2 ; and if R^{13} is Cl or Br, then R^9 may also represent (C_{1-3}) alkyl;

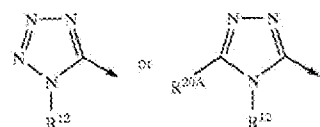
R^{10} , R^{11} are independently of each other selected from the group consisting of H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl- (C_{1-3}) alkyl, (C_{2-6}) alk-

enyl, $O-(C_{1-6})$ alkyl, $S-(C_{1-6})$ alkyl, halo, CF_3 , OCF_3 , OH, NO_2 , CN, $-NR^{21}R^{22}$, $-C(O)R^{21}$, $-(C_{1-3})$ alkyl- $C(O)R^{21}$, $-C(O)OR^{22}$, $-(C_{1-3})$ alkyl- $C(O)OR^{22}$, $-SO_2-(C_{1-3})$ alkyl- $C(O)OR^{22}$, wherein R^{21} is (C_{1-4}) alkyl and R^{22} is H or (C_{1-4}) alkyl;

$-(C_{1-3})$ alkyl- $C(O)NH_2$, $C(O)NH_2$, $S(O)-(C_{1-6})$ alkyl, $-SO_2-(C_{1-6})$ alkyl, $-SO_2$ -phenyl, $-SO_2-NH_2$, phenyl, phenylmethyl, 2-, 3- or 4-pyridinyl, 1-pyrrolyl, whereby said phenyl, pyridinyl and pyrrolyl may have one or more substituents selected from the group consisting of halo, NO_2 , C_{1-3} -alkyl and CF_3 ;

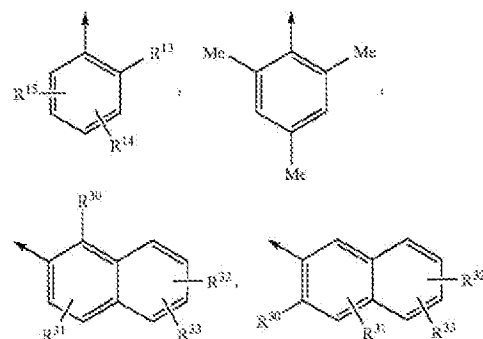
or a pharmaceutically acceptable salt thereof.

18. The compound of formula 1 according to claim 17 wherein Ar^2 is



and

wherein R^{12} is selected from the group consisting of



wherein R^{13} , R^{14} , R^{15} , R^{20A} , R^{30} , R^{31} , R^{32} and R^{33} are as defined in claim 17.

19. The compound of formula 1 according to claim 18 wherein

R^{13} represents Cl or Br and

if R^9 is NO_2 , Cl or Br, then R^{15} may also represent F or CH_3 ;

R^{14} , R^{15} ,

R^{31} , R^{32} ,

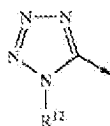
R^{33} are each independently selected from the group consisting of H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl- (C_{1-3}) alkyl, (C_{2-6}) alkenyl, $O-(C_{1-4})$ alkyl, $S-(C_{1-4})$ alkyl, halo, CF_3 , OCF_3 , OH, NO_2 , CN, SO_2NH_2 , $SO_2-(C_{1-4})$ alkyl, $C(O)OR^1$ wherein R^1 is H or (C_{1-4}) alkyl, or NR^2R^3 wherein R^2 and R^3 each independently is H or (C_{1-4}) alkyl; and

R^{30} represents Cl or Br.

20. The compound of formula 1 according to claim 19 wherein W is $\text{CH}_2\text{C}(\text{O})\text{NH}$.

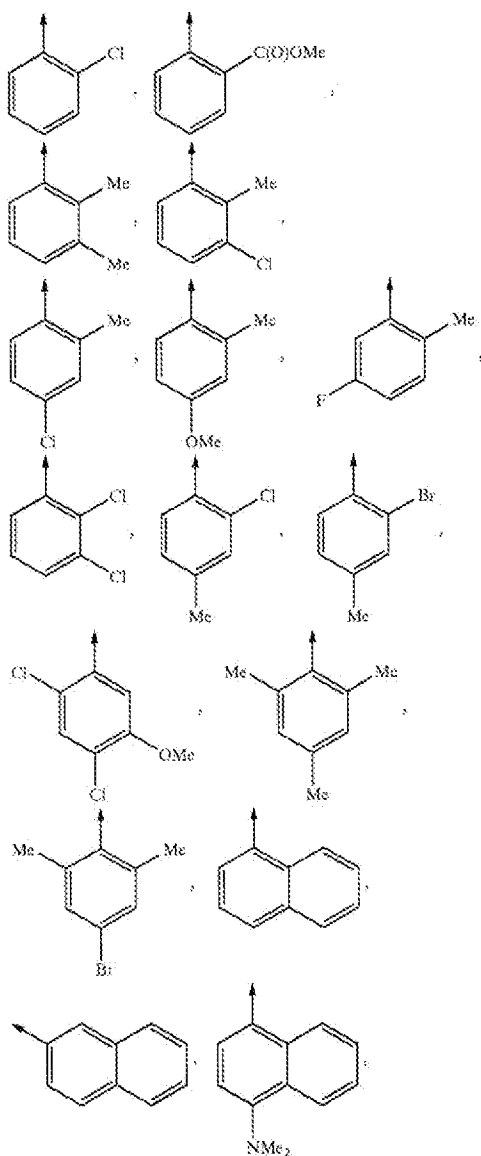
21. A compound according to claim 17 wherein

Ar^1 is defined as

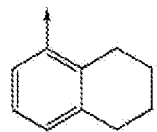


and

wherein R^{12} is selected from the group consisting of



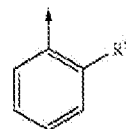
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X is S;

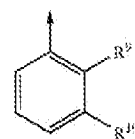
W is $\text{CH}_2\text{C}(\text{O})\text{NR}^6$ wherein R^6 is H or (C_{1-4}) alkyl; and

Ar^2 is



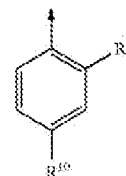
wherein R^9 is halo or NO_2 ; or

Ar^2 is



wherein R^9 is halo or NO_2 and R^{10} is halo; or

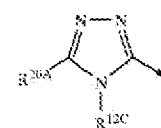
Ar^2 is



wherein R^9 is halo or NO_2 , and R^{10} is OMe, halo, OH, NO_2 , phenyl, $\text{C}(\text{O})\text{OH}$ or $\text{C}(\text{O})\text{OMe}$.

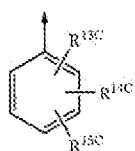
22. A compound according to claim 17

wherein Ar^1 is

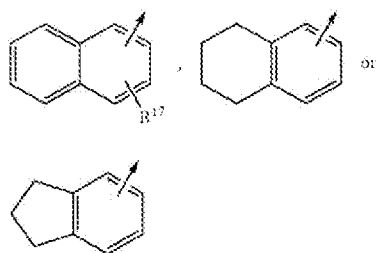


and

wherein R^{13C} is a phenyl of formula

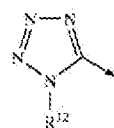


wherein R^{13C} , R^{14C} and R^{15C} each independently represents H, Me, Et, Pr, iPr, tBu, OMe, OEt, SMe, SEt, Br, Cl, F, CF_3 , NO_2 , $C(O)OH$, $C(O)OMe$ or $C(O)OEt$, provided that at least one of R^{13C} , R^{14C} and R^{15C} is other than hydrogen; or R^{13C} is

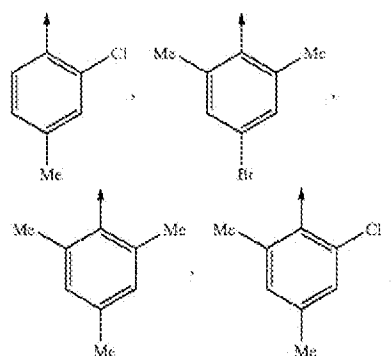


wherein R^{17} is selected from H, Me, OMe, Cl, F, CF_3 , NH_2 , $NHMe$ or NMe_2 ; and R^{20A} is H, Me, Et, Pr or iPr.

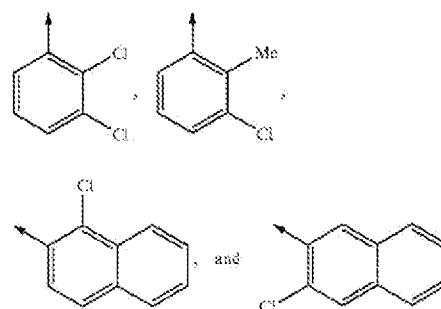
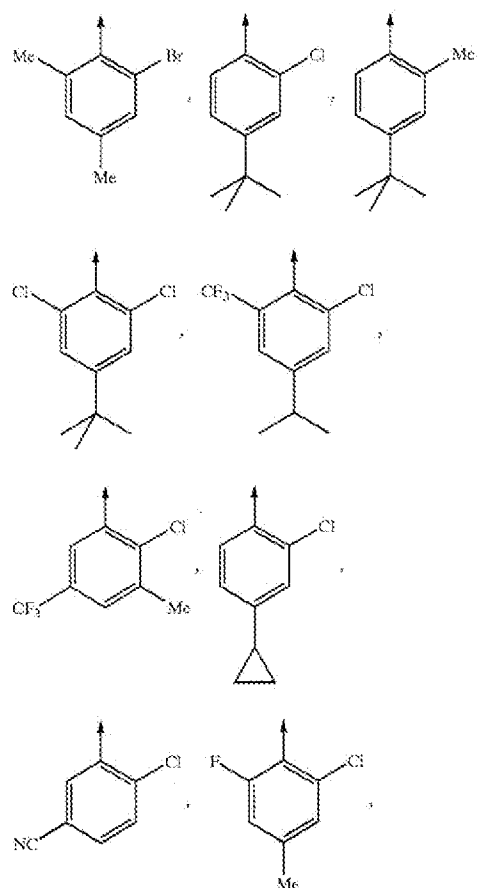
23. A compound of formula 1, according to claim 17, wherein Ar^1 is:



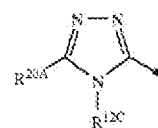
and wherein R^{12} selected from the group consisting of:



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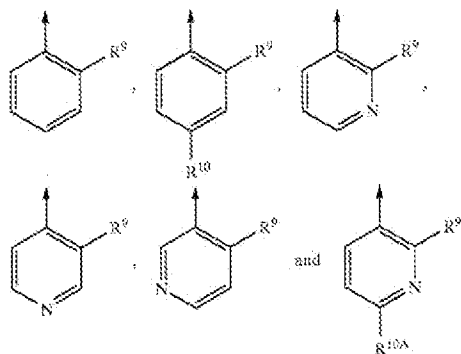
24. A compound according to claim 23, wherein Ar^1 is:



wherein R^{12C} is defined as R^{12} in claim 23 and R^{20A} is methyl.

25. A compound of formula 1, according to claim 17, wherein

Ar^2 is selected from the group consisting of



wherein R^9 is C_1 or NO_2 and

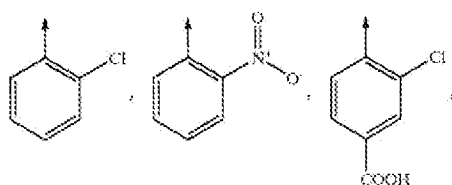
R^{10A} is C_{1-6} alkyl;

R^{10} is selected from the group consisting of (C_{1-4}) alkyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl- (C_{1-3}) alkyl, (C_{2-6}) alkenyl, $O(C_{1-6})$ alkyl, $S(C_{1-6})$ alkyl, halo, CF_3 , OCF_3 , OH , NO_2 , CN , $-NR^{N1}R^{N2}$, $-C(O)R^{21}$, $-(C_{1-3})$ alkyl- $C(O)R^{21}$, $-C(O)OR^{22}$, $-(C_{1-3})$ alkyl- $C(O)OR^{22}$, $-SO_2-(C_{1-3})$ alkyl- $C(O)OR^{22}$, $-(C_{1-3})$ alkyl- $C(O)NH_2$, $C(O)NH_2$, $-S(O)-(C_{1-6})$ alkyl, $-SO_2-(C_{1-6})$ alkyl, $-SO_2$ -phenyl, $-SO_2-NH_2$, phenyl, phenylmethyl, phenyl- SO_2 -, 2-, 3- or 4-pyridinyl, 1-pyrrolyl, whereby said phenyl, pyridinyl and pyrrolyl may have one or more substituents selected from the group consisting of halo, NO_2 , C_{1-3} -alkyl and CF_3 ;

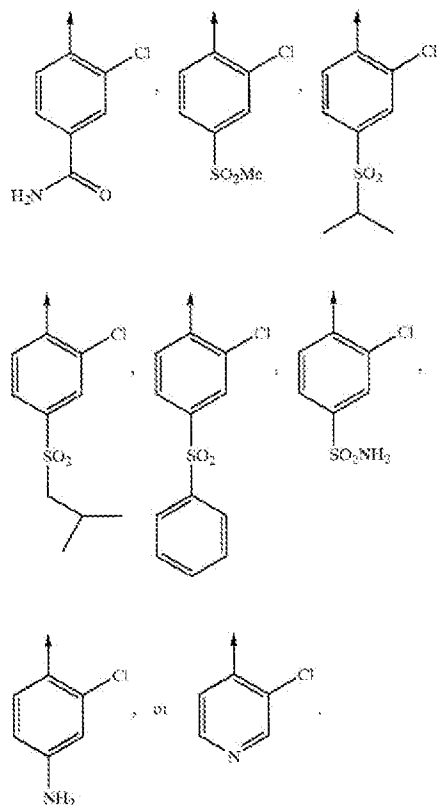
wherein R^{21} is (C_{1-6}) alkyl and R^{22} is H or (C_{1-4}) alkyl;

wherein R^{N1} , R^{N2} each independently represent H or (C_{1-6}) alkyl, whereby R^{N1} and R^{N2} may be covalently bonded to each other to form together with the N-atom to which they are attached to a 4 to 7-membered heterocycle whereby the $-CH_2-$ group at the position 4 of a 6 or 7-membered heterocycle may be replaced by $-O-$, $-S-$ or $-NR^{N3}-$ wherein R^{N3} represents H, $-C(O)OR^{22}$, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{3-7}) cycloalkyl- (C_{1-3}) alkyl, wherein R^{22} is H or (C_{1-4}) alkyl.

26. A compound of formula 1, according to claim 25, wherein Ar^2 is:



-continued



27. A pharmaceutical composition comprising a compound of formula 1 as defined in claim 1, or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable carriers.

28. A pharmaceutical composition comprising a compound of formula 1 as defined in claim 17, or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable carriers.

29. A pharmaceutical composition for the treatment of HIV infection, comprising a compound of formula 1 as defined in claim 1, or a pharmaceutically acceptable salt thereof.

30. A pharmaceutical composition for the treatment of HIV infection, comprising a compound of formula 1 as defined in claim 17, or a pharmaceutically acceptable salt thereof.

31. A process for preparing a compound of formula 1 wherein Ar^1 and Ar^2 are as defined in claim 1, X is S or O and W is $(CR^5R^{5A})_{1-2}C(O)NR^6$, wherein R^5 , R^{5A} and R^6 each independently is H or (C_{1-6}) alkyl, comprising:

a) reacting a thiol or alcohol of formula Ar^1-X-H with an ω -halo alkanolic alkyl ester of formula $Y-(CR^5R^{5A})_{1-2}C(O)OR^A$ wherein Y is halo and R^A is (C_{1-6}) alkyl, in the presence of a base, to obtain the

corresponding ester of formula $\text{Ar}^1\text{---X---}(\text{CR}^5\text{R}^6)_{1-2}\text{C(O)OR}^A$, followed by hydrolysis of the ester to the corresponding acid wherein $\text{R}^A=\text{H}$, and coupling the latter acid with an aromatic amine of general formula $\text{HNR}^6\text{---Ar}^2$ in the presence of a coupling agent to obtain the corresponding compound of formula 1 wherein Ar^1 , Ar^2 , X and W are as defined in this claim; or

b) reacting a thiol or alcohol of formula $\text{Ar}^1\text{---X---H}$ wherein Ar^1 and X are as defined in this claim with an anilide of formula $\text{Y---}(\text{CR}^5\text{R}^6)_{1-2}\text{C(O)NR}^6\text{---Ar}^2$ wherein Y, R^5 , R^6 and Ar^1 are as defined in this claim, in the presence of a base to obtain the corresponding compound of formula 1.

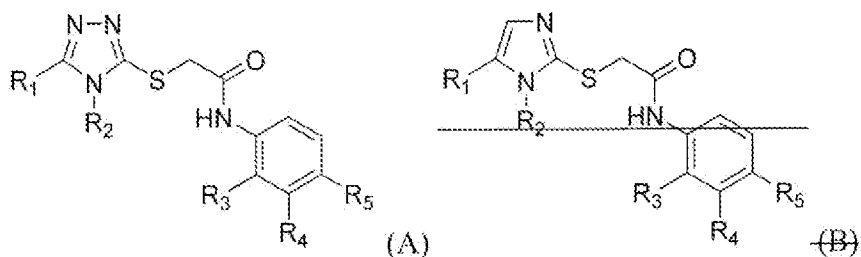
* * * * *

Exhibit B

Complete Listing of Claims in Supplemental Response to Final Office Action:

1-21. (Canceled)

22. (Withdrawn) A method of treating an HIV infected patient comprising administering to the patient a pharmaceutical composition comprising a compound in a dose effective to reduce viral propagation wherein the compound has a structure according to Formula (A) ~~or Formula (B)~~



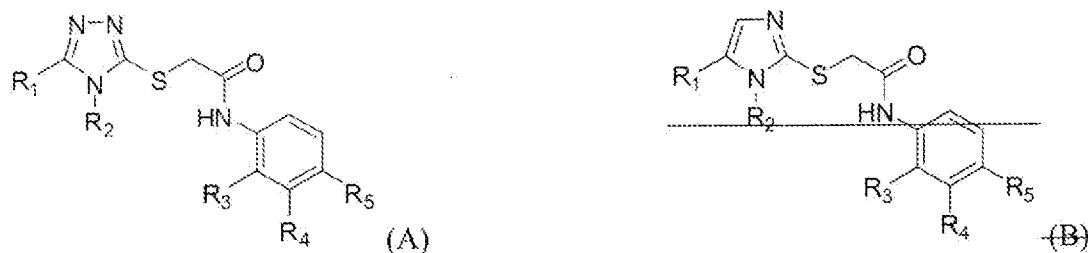
wherein R_1 is optionally substituted lower alkyl, halogen, or CF_3 ,

R_2 is ~~a substituted naphthyl optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted quinoline, or optionally substituted isoquinoline;~~ and

R_3 , R_4 , and R_5 are independently hydrogen, halogen, optionally substituted alkyl, S-alkyl, CF_3 , heterocycle, $NR'R''$, $S(O)_2R'$, or $C(O)R'$, and wherein R' and R'' are independently NH_2 , $NHalkyl$, $NHAcyl$, $NalkylAcyl$, $N(Alkyl)_2$, O-alkyl, acyl, aryl, alkyl, heterocycle, or R' and R'' form a ring.

23-45. (Canceled)

46. (Currently Amended) A compound having a structure according to Formula (A) ~~or (B)~~



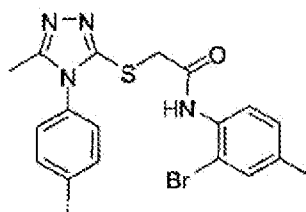
wherein R_1 is optionally substituted lower alkyl, or halogen,

~~R₂ is a substituted naphthyl selected from the group consisting of a monosubstituted naphthyl, a disubstituted naphthyl, or a trisubstituted naphthyl, a monosubstituted quinoline, a disubstituted quinoline, a trisubstituted quinoline, a monosubstituted isoquinoline, a disubstituted isoquinoline, and a trisubstituted isoquinoline; and~~
R₃, R₄, and R₅ are independently hydrogen, halogen, optionally substituted alkyl, S-alkyl, CF₃, heterocycle, NR'R'', S(O)₂R', or C(O)R', and wherein R' and R'' are independently NH₂, NHAkyl, NHAkyl, N(Alkyl)₂, O-alkyl, acyl, aryl, alkyl, heterocycle, or R' and R'' form a ring,

or a pharmacologically acceptable salt thereof.

47-51. (Canceled).

52. (Previously Presented) A compound having the following chemical structure



53. (New) The compound of claim 46, wherein R₂ is a mono-substituted naphthyl.